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Original Articles

VARIATIONS IN THE SPECIFICITY OF SKIN-SENSITIZING ANTIBODIES IN THE ALLERGY OF MAN, AS SHOWN BY NEUTRALIZATION WITH ANTIGENS*

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THE neutralization of the Prausnitz-Küstner skin-sensitizing antibody by the specific antigen has frequently been used as a means of studying the mechanism of sensitivity and protection in allergic diseases and also as a method of establishing the identity or group relationship of various antigens. Considering the extent to which it has been used, very little work has been done to determine the degree of specificity of the phenomenon.

When the neutralization reaction was described by Coca and Grove,[1] they showed that it could be carried out either by injecting a mixture of antigen and serum made in a test tube, or by injecting first serum and then antigen into the skin of a normal subject. Using a serum sensitive to both timothy and ragweed pollens, they found that neutralization in vivo with either of these antigens did not affect the reaction to the other. With another serum sensitive to cotton and kapok seeds, they showed that sites exhausted with cottonseed did not react on test with kapok seed, but neutralization with kapok did not affect the reaction to cottonseed. Between various grass pollens, there was complete cross-neutralization. The same was true between giant and low ragweed. They considered that the reaction was specific and could be used to determine the identity of antigens. Further studies by Levine and Coca[2] placed the neutralization on a more quantitative basis and again showed that ragweed pollen extract would not neutralize the reactions of serum to timothy.

On this basis, the reaction was accepted as a means of studying the specificity of antigens. The in vivo method was employed in establishing the identity of the various grass pollen antigens,[3, 4] in studying low and giant ragweed[5-7] and to show the relationship between the fractions of egg protein.[8]

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In 1930, Walzer and Bowman[9] showed the advantages of making mixtures in vitro and by this method showed cross reactions between donkey, horse, and zebra epithelia. This type of procedure has also been used to determine the relationships of grass pollens,[10] giant and low ragweed,[11] fungi,[12] and food antigens.[13]

On the other hand, cases of nonspecific cross-neutralization between antigens of different biological sources have been described. Clarke[14] showed that a strong reaction of one antigen in a passive transfer site might render the site inactive on subsequent tests with other antigens. His experiments suggested that the cross-neutralization depended on the relative concentrations of the antibodies. Harkavy and Witebsky[15] reported studies of a serum of which the reaction to corn pollen was neutralized by mixture with timothy pollen or tobacco. They considered the corn antibody was not an independent antibody but related to those for timothy and tobacco.

The present investigation is a study of the specificity of neutralization, the extent to which one antigen can neutralize an allergic serum so that it will not react with other antigens. For convenience in describing the results, this is spoken of as *cross-neutralization* as opposed to *direct* or *specific* neutralization, in which the same antigen is used for neutralizing and testing. Where two antigens produced cross-neutralization to each other in the same serum, they are said to show *reciprocal* cross-neutralization. Where one antigen neutralizes to test with the second, but the latter does not neutralize the same serum to test with the former, the cross reaction is *unilateral.*

METHODS

The serums used were obtained from *untreated* patients with typical allergic rhinitis, many of whom also had asthma. On passive transfer, each serum showed definite reactions to two or more of the common inhalant antigens. No food antigens were used because the reactions might be affected by the diet of the test subject, which could not be rigidly controlled.

The antigen solutions were buffered saline extracts, standardized on a protein nitrogen basis (0.00001 mg. protein nitrogen = 1 unit). Equal volumes of serum and antigen extract were mixed in vitro, according to the quantitative technique used in previous experiments[11] at this clinic. Each mixture was injected into two or more sites in the skin of the back of a healthy (nonallergic) test subject who gave negative intradermal tests to the antigens used. The duplicate sites were tested after forty-eight hours with different antigens, using 0.025 c.c. of the 1,000 unit per cubic centimeter dilution.

It was found that the reactions of sites were sometimes affected by other mixtures injected into the test subject at the same time. When high concentrations of an actively neutralizing antigen were used in

several mixtures, control sites (containing only serum and saline) in the same test subject might not react on test. Apparently enough of the antigen might spread through the circulation to neutralize the control sites. This difficulty could be avoided by determining in advance the approximate amount of antigen needed to neutralize the particular serum, and avoiding the use of a great excess.

In most cases, the serums used in cross-neutralization tests were also titrated by the dilution method to determine the relative sensitivity to the various antigens used.[16] Although the actual end point of dilution tests varied in the skin of different test subjects, the relative reaction to two antigens was readily determined by making duplicate sites in the same test subject. Dilution and neutralization experiments were not done on the same test subject since it was found that the serum dilutions might be neutralized by high concentration of antigen in nearby sites.

EXPERIMENTAL RESULTS

Animal Danders.—Since patients sensitive to animal danders usually reacted to epithelia of related species, they were suitable for cross-neutralization experiments.

Six serums from cases clinically sensitive either to dog or cat danders, reacted on passive transfer with both of these antigens. Five of these serums were neutralized by one or both antigens in the range of concentrations used (1000-5000 units per cubic centimeter). Where there was

PROTOCOL 1. SERUM AM. CLINICALLY VERY SENSITIVE TO DOG

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. CAT EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. CAT EP.
1	Dog Ep.	100	+	0	Conc.	++++	+++
2	Dog Ep.	1000	0	0	1-10	+++	++
3	Dog Ep.	5000	0	0	1-100	++	+
4	Cat Ep.	100	++++	++	1-1000	0	0
5	Cat Ep.	1000	++++	++			
6	Cat Ep.	5000	++++	+			
7	Saline		++++	++			

PROTOCOL 2. SERUM FI. CLINICALLY VERY SENSITIVE TO CAT

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. CAT EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. CAT EP.
1	Dog Ep.	100	++	+++	Conc.	+	+++
2	Dog Ep.	1000	++	+++	1-10	0	++
3	Dog Ep.	5000	+	+++	1-100	0	0
4	Cat Ep.	100	0	±			
5	Cat Ep.	1000	0	0			
6	Cat Ep.	5000	0	0			
7	Saline		++	++++			

direct neutralization, there was also cross-neutralization to test with the other antigen. In the sixth case, which was clinically *slightly* sensitive to dog, neither dander extract neutralized at a strength of 1000 units per cubic centimeter. Protocols 1, 2, and 3 are typical of the reactions obtained in the cases showing neutralization.

PROTOCOL 3. SERUM PA. MODERATELY SENSITIVE TO DOG AND CAT

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	CAT EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	CAT EP.
1	Dog Ep.	100	+	+++	Conc.	+++	+++
2	Dog Ep.	1000	±	+	1-10	+	++
3	Dog Ep.	5000	0	0	1-100	0	±
4	Cat Ep.	100	±	0	1-1000	0	0
5	Cat Ep.	1000	0	0			
6	Cat Ep.	5000	0	0			
7	Saline		++	+++			

It is apparent that the type of cross reaction varied according to the serum used, depending on the relative clinical sensitivity to the two antigens, which was paralleled by the activity of the passive transfer reactions and the dilution tests. The first two protocols illustrate unilateral cross-neutralization by dog and cat, respectively, the third is an example of reciprocal cross-neutralization.

Two serums were studied with horse and cow danders. Both were obtained from patients clinically very sensitive to horses, but who did not know whether or not cows affected them. Results were essentially similar in the two cases, both of which showed reciprocal cross-neutralization, so only one protocol is given.

PROTOCOL 4. SERUM AD. CLINICALLY VERY SENSITIVE TO HORSE

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. HORSE EP.	COW EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. HORSE EP.	COW EP.
1	Horse Ep.	100	0	0	Conc.	++++	++++
2	Horse Ep.	1000	0	0	1-10	+++	+++
3	Horse Ep.	5000	0	0	1-100	++	++
4	Cow Ep.	100	+++	++	1-1000	0	0
5	Cow Ep.	1000	++	+			
6	Cow Ep.	5000	0	0			
7	Saline		+++	++			

The cross reactions between dog and horse danders were studied with four serums. Here the antigens are biologically less closely related than in the groups described above, as they come from different orders of mammals. Protocols for three of the serums are given, the reactions in the fourth case were similar to those of Protocol 7.

PROTOCOL 5. SERUM AM. CLINICALLY VERY SENSITIVE TO DOG

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	HORSE EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	HORSE EP.
1	Dog Ep.	100	+	0	Conc.	++++	++
2	Dog Ep.	1000	0	0	1-10	+++	±
3	Horse Ep.	100	++++	+	1-100	+++	0
4	Horse Ep.	1000	++++	+	1-1000	+	0
5	Horse Ep.	5000	++++	+			
6	Saline		++++	+			

PROTOCOL 6. SERUM AD. CLINICALLY VERY SENSITIVE TO HORSE, SLIGHTLY SENSITIVE TO DOG

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	HORSE EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	HORSE EP.
1	Dog Ep.	100	++	++++	1-10	+++	++++
2	Dog Ep.	1000	++	++++	1-100	+	+++
3	Horse Ep.	10	0	++	1-1000	0	0
4	Horse Ep.	100	0	+			
5	Horse Ep.	1000	0	0			
6	Saline		++	++++			

PROTOCOL 7. SERUM JE. MODERATELY SENSITIVE TO HORSE AND DOG

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	HORSE EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	HORSE EP.
1	Dog Ep.	100	++	+	Conc.	++	++
2	Dog Ep.	1000	0	+	1-10	+	±
3	Dog Ep.	5000	0	+	1-100	0	0
4	Horse Ep.	100	+++	0	1-1000	0	0
5	Horse Ep.	1000	+++	0			
6	Saline		+++	+++			

As in the case of cat and dog, where one antigen was much more active, clinically and by dilution test, there was unilateral cross-neutralization. However, where the sensitivity to the two antigens was approximately the same, each antigen produced specific neutralization and there

PROTOCOL 8. SERUM AD. CLINICALLY VERY SENSITIVE TO HORSE

NEUTRALIZATION				
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. HORSE EP.	CAT EP.
1	Horse Ep.	10	++	0
2	Horse Ep.	100	+	0
3	Horse Ep.	1000	0	0
4	Cat Ep.	100	++++	+
5	Cat Ep.	100	+++	+
6	Saline		++++	++

was no cross-neutralization in the concentrations used. Serums tested with horse and cat (Protocol 8) or with dog and cow gave similar results.

The serum of a case reacting with horse and rabbit danders (and clinically sensitive to both), also showed specific neutralization by each antigen without cross reactions in the range of concentration used (Protocol 9).

PROTOCOL 9. SERUM HA. SENSITIVE TO HORSE AND RABBIT CLINICALLY

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. RABBIT EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. HORSE EP.	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. RABBIT EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. HORSE EP.
1	Rabbit Ep.	100	+++	++	Conc.	++	+
2	Rabbit Ep.	1000	++	++	1-10	0	0
3	Rabbit Ep.	5000	0	+	1-100	0	0
4	Horse Ep.	100	+++	+			
5	Horse Ep.	1000	+++	±			
6	Horse Ep.	5000	+++	0			
7	Saline		+++	+			

POLLENS

Twelve serums were studied which showed passive transfer reactions to both timothy *(Phleum pratense)* and low ragweed *(Ambrosia artemisiaefolia)* pollens. Of these, five gave clinical histories of early hay fever alone, five of late hay fever alone, and two of rhinitis during both seasons. The activity of the passive transfer reactions and the dilution tests paralleled the relative clinical importance of the pollens as indicated by the history. In this group particularly, many of the slight reactions obtained on simple passive transfer failed to appear in neutralization experiments when relatively large amounts of the more active antigen were used in other sites on the same test subject. As previously stated, this was attributed to neutralization of the serum site by antigen carried through the circulation. Three of the timothy cases and two of the ragweed group were unsatisfactory because of this difficulty.

The following three protocols are typical of the results obtained in the three groups of cases.

PROTOCOL 10. SERUM DIM. LATE HAY FEVER

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. TIMOTHY	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. TIMOTHY
1	Low R.	100	0	0	Conc.	++++	++++
2	Low R.	200	0	0	1-10	+++	+++
3	Tim.	100	++++	++	1-100	+++	+
4	Tim.	300	++++	++	1-1000	±	0
5	Tim.	1000	++++	++			
6	Saline		++++	+++			

PROTOCOL 11. SERUM BA. EARLY HAY FEVER

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. TIMOTHY	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. TIMOTHY
1	Low R.	100	0	±	Conc.	0*	++++
2	Low R.	1000	0	0	1-10	0	+++
3	Tim.	100	+	+++	1-100	0	+
4	Tim.	300	+	+++	1-1000	0	±
5	Saline		+	++			

*This serum gave a passive transfer reaction to ragweed in the test subject used for neutralization, and in one other, but not in the subject used for the dilution test. Obviously the reaction to ragweed was much less than that to timothy.

PROTOCOL 12. SERUM BE. EARLY AND LATE HAY FEVER

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. TIMOTHY	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. TIMOTHY
1	Low R.	100	0	+	Conc.	+++	+++
2	Low R.	1000	0	+	1-10	+	+
3	Tim.	100	++	0	1-100	0	0
4	Tim.	1000	++	0	1-1000	0	0
5	Saline		+++	++			

It was found that cases clinically sensitive to only one of the pollens showed unilateral cross reactions. Where there was a marked sensitivity to both, the neutralizations were specific. This case corresponds to that described by Coca and Grove.[1]

Cross-neutralization between low ragweed and various other weeds was also studied and numerous cross reactions observed. Because of the overlapping seasons of pollination and irregular geographical distribution of these plants, it was not always possible to be sure which were

PROTOCOL 13. SERUM HO. NEW YORK

NEUTRALIZATION						DILUTIONS			
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW R.	*Chenopod.*	CAR. WD.*	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW R.	*Chenopod.*	CAR. WD.*
1	Low R.	100	+	0	0	Conc.	++++	++	+
2	Low R.	300	0	0	0	1-10	+++	+	+
3	*Chenop.*	100	++++	++	++	1-100	++	0	0
4	*Chenop.*	1000	++++	++	++	1-1000	0	0	0
5	*Chenop.*	5000	++++	0	0				
6	Car. Wd.*	100	++++	+	+				
7	Car. Wd.	1000	++++	+	+				
8	Car. Wd.	5000	++++	++	++				
9	Saline		++++	++	++				

*Careless Weed.

actual causes of hay fever in the patients from whom the serums were obtained. Therefore, the activity of the passive transfer skin reactions and the dilution tests furnished the chief evidence of the relative sensitivity to the different pollens. A few typical protocols are given with the geographical location indicated.

In the case of Ho, low ragweed seems to be more active than careless weed *(Amaranthus palmieri)* or chenopod *(Chenopodium album)*, but in the case of Pa, ragweed is the least active antigen.

PROTOCOL 14. SERUM PA. WYOMING

NEUTRALIZATION						DILUTIONS			
			REACTION ON TEST WITH 1000 UNITS PER C.C.				REACTION ON TEST WITH 1000 UNITS PER C.C.		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	LOW R.	*Chenopod.*	CAR. WD.*	SERUM DILUTION	LOW R.	*Chenopod.*	CAR. WD.*
1	Low R.	100	+++	++++	+++	Conc.	++	+++	+++
2	Low R.	1000	+	++++	+++	1-10	++	+++	+++
3	*Chenop.*	100	0	++	++	1-100	0	++	+
4	*Chenop.*	1000	0	+	++	1-1000	0	0	0
5	Car. Wd.*	100	0	++	+++				
6	Car. Wd.	1000	0	+	0				
7	Saline		+++	+++	+++				

*Careless weed.

Protocols 15 and 16 are examples of cross reactions between low ragweed and *Iva ciliata* pollens. The serum St. was from a New York

PROTOCOL 15. SERUM ST. NEW YORK

NEUTRALIZATION					DILUTIONS			
			REACTION ON TEST WITH 1000 UNITS PER C.C.			REACTION ON TEST WITH 1000 UNITS PER C.C.		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	LOW RAGWEED	*Iva*	SERUM DILUTION	LOW RAGWEED	*Iva*
1	Low R.	100	+	0	Conc.	++++	+++
2	Low R.	1000	0	0	1-10	+++	+++
3	*Iva*	100	+++	++	1-100	+++	+
4	*Iva*	1000	++	+	1-1000	+	0
5	Saline		+++	++			

PROTOCOL 16. SERUM CL. TEXAS

NEUTRALIZATION				
			REACTION ON TEST WITH 1000 UNITS PER C.C.	
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	LOW RAGWEED	*Iva*
1	Low R.	100	++	++++
2	Low R.	1000	0	+++
3	*Iva*	100	+++	++
4	*Iva*	1000	+	0
5	Saline		++++	++++

patient with late hay fever, who showed greater reactions to low ragweed than to *Iva* pollen on intradermal test. The Cl. serum, kindly supplied by Dr. Homer E. Prince, was from a Texas patient who, by intradermal test, was more sensitive to *Iva* than to low ragweed.

Protocols 17 and 18 show neutralization experiments with serums of late hay fever patients, who in addition to ragweed, reacted on test with cocklebur *(Xanthium canadense)* and sage brush *(Artemisia tridentata)*, respectively.

PROTOCOL 17. SERUM SH. NEW YORK

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. COCKLEBUR	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. COCKLEBUR
1	Low R.	100	+	0	Conc.	++++	+++
2	Low R.	300	0	0	1-10	+++	+++
3	Low R.	1000	0	0	1-100	+++	++
4	Cockle.*	100	++++	+	1-1000	+	0
5	Cockle.	300	++++	±			
6	Cockle.	1000	++++	0			
7	Saline		++++	+++			

*Cocklebur.

PROTOCOL 18. SERUM BA. NEW YORK

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. SAGEBRUSH	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	REACTION ON TEST WITH 1000 UNITS PER C.C. SAGEBRUSH
1	Low R.	100	0	0	Conc.	++++	+++
2	Low R.	1000	0	0	1-10	+++	+++
3	Sageb.*	100	++++	+	1-100	+++	+
4	Sageb.	1000	++++	+	1-1000	±	0
5	Sageb.	5000	++++	+			
6	Saline		++++	+			

*Sagebrush.

The following protocol shows neutralization by timothy pollen of reactions to some botanically unrelated pollens. The serum was taken

PROTOCOL 19. SERUM AM.

NEUTRALIZATION								
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. TIMOTHY	LOW RAGWEED	OAK	HICKORY	PLANTAIN	SORREL
1	Tim.*	1000	0	++	0	0	±	0
2	Low R.	1000	++++	+	+++	+++	+++	+++
3	Oak	1000	++++	+++	0	+	+++	+++
4	Saline		++++	+++	+++	+++	+++	+++

*Timothy.

from a patient with perennial asthma and multiple reactions to pollens and other inhalants. By intradermal test as well as by passive transfer, the reaction to timothy was greater than to the other pollens.

SEED ANTIGENS

The serums of a few patients sensitive to cottonseed, kapokseed and flaxseed were studied. All of the cases reacting with kapokseed gave as strong or stronger reactions to test with cottonseed. They were clinically sensitive to cottonseed, but it was often difficult to tell whether kapok was a cause of symptoms.

One case was apparently only slightly sensitive to cottonseed and kapok. With this serum, no specific or cross-neutralization was obtained with either antigen in concentrations of 1,000 units per cubic centimeter.

PROTOCOL 20. SERUM BAC.

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. COTTONSEED	KAPOK	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. COTTONSEED	KAPOK
1	Cotton	100	+++	+++	1-10	+	+
2	Cotton	1000	++	++	1-100	0	0
3	Kapok	100	++	++	1-1000	0	0
4	Kapok	1000	+	+			
5	Saline		++	+++			

Protocol 21 is typical of the cases acutely sensitive to cottonseed. The results are consistent with those obtained by Coca and Grove[1] by the in vivo method.

PROTOCOL 21. SERUM NA. CLINICALLY VERY SENSITIVE TO COTTONSEED

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. COTTONSEED	KAPOK	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. COTTONSEED	KAPOK
1	Cotton	10	+	0	1-10	+++	+
2	Cotton	100	0	0	1-100	++	0
3	Kapok	10	++++	++	1-1000	0	0
4	Kapok	100	++++	++			
5	Kapok	500	++++	++			
6	Saline		++++	++			

One serum, from a case very sensitive to seeds and nuts, was studied with flaxseed and cottonseed. Both showed specific neutralization, without cross reaction.

It may be noted from Protocols 21 and 22 that the very active seed antigens neutralized in a lower range of concentrations than most of the danders and pollens.

PROTOCOL 22. SERUM HON. CLINICALLY SENSITIVE TO SEEDS AND NUTS

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. COTTONSEED	REACTION ON TEST WITH 1000 UNITS PER C.C. FLAXSEED	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. COTTONSEED	REACTION ON TEST WITH 1000 UNITS PER C.C. FLAXSEED
1	Cotton	10	0	++	1-10	++	++
2	Cotton	100	0	++	1-100	+	+
3	Cotton	500	0	+	1-1000	0	0
4	Flax	10	+++	++			
5	Flax	100	++	0			
6	Flax	500	+	0			
7	Saline		+++	++			

CROSS NEUTRALIZATION BETWEEN BIOLOGICALLY UNRELATED ANTIGENS

In a few cases, active antigens were found to neutralize the reactions of serums to test with antigens of very different biological origin. The following protocols show striking examples.

PROTOCOL 23. SERUM AD. CLINICALLY VERY SENSITIVE TO HORSE AND SLIGHTLY SENSITIVE TO RAGWEED

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. HORSE EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. HORSE EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED
1	Horse	100	±	0	1-10	++++	+
2	Horse	1000	0	0	1-100	+++	±
3	Low R.	100	++++	+	1-1000	0	0
4	Low R.	1000	++++	+			
5	Low R.	5000	++++	+			
6	Saline		++++	+			

PROTOCOL 24. SERUM ADM. LATE HAY FEVER LASTING AFTER FROST. SKIN TESTS TO RAGWEED AND ALTERNARIA MARKED

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. *Alternaria*	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. *Alternaria*	REACTION ON TEST WITH 1000 UNITS PER C.C. LOW RAGWEED
1	*Alter.**	100	++	±	Conc.	+++	++
2	*Alter.*	1,000	0	0	1-10	++	0
3	Alter.	10,000	0	0	1-100	0	0
4	Low R.	100	+++	+	1-1000	0	0
5	Low R.	1,000	+++	±			
6	Low R.	5,000	+++	0			
7	Saline		+++	++			

**Alternaria.*

SUMMARY OF EXPERIMENTAL RESULTS

As shown by the protocols, cross-neutralization between different antigens occurred very frequently. Most of the cross reactions were unilateral, with one antigen neutralizing a serum to test with another, but

PROTOCOL 25. SERUM AM. CLINICALLY VERY SENSITIVE TO DOG, NO DEFINITE CLINICAL HISTORY OF HICKORY HAY FEVER

NEUTRALIZATION					DILUTIONS		
MIXTURE NUMBER	SERUM MIXED WITH	UNITS PER C.C.	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. HICKORY	SERUM DILUTION	REACTION ON TEST WITH 1000 UNITS PER C.C. DOG EP.	REACTION ON TEST WITH 1000 UNITS PER C.C. HICKORY
1	Dog Ep.	100	+	±	Conc.	++++	++
2	Dog Ep.	1000	0	0	1-10	++++	+
3	Dog Ep.	5000	0	0	1-100	+++	0
4	Hick.*	100	+++	++	1-1000	0	0
5	Hick.	1000	+++	++			
6	Hick.	5000	+++	+			
7	Saline		++++	++			

*Hickory.

the latter not affecting the reaction of the same serum with the former. In a few cases, reciprocal cross-neutralization was noted, where each of two antigens neutralized the serum to test with the other.

Throughout the experiments it was found that antigens to which the patient was clinically very sensitive and to which the serum gave very strong passive transfer reactions, usually persisting in high serum dilutions, neutralized in low concentrations, for example, cottonseed and flaxseed in Protocols 21 and 22. On the other hand, antigens to which the patient showed little or no clinical sensitivity, and to which the serum gave small reactions, neutralized at high concentration or not at all.

The unilateral type of cross-neutralization occurred where one of the antigens used reacted much more strongly with the serum than the other. In all cases the relative activities of the antigens on passive transfer corresponded quite closely to the dilution tests and the clinical history of the patient. The more active antigen neutralized the reaction of the serum to test with both antigens, while the less active often showed no neutralization in the range of concentrations used. This type of cross reaction is illustrated by Protocols 1 and 2. It occurred between most of the animal danders, many of the pollens, cotton and kapok seeds, when one antigen reacted more strongly with the serum. In a few cases unilateral cross-neutralization occurred between unrelated substances such as horse dander and ragweed pollen (Protocol 23) or dog dander and hickory pollen (Protocol 25), but these must be considered rather exceptional cases.

In some cases the less active antigen produced specific neutralization while the more active showed both direct and cross-neutralization (Protocol 17). As might be expected from the failure of weakly reacting antigens to cause cross-neutralization, antigens to which a serum did not give a passive transfer reaction did not neutralize reactions to other antigens.

In the case of serums which reacted strongly to one antigen and less actively to several others, the most active antigen usually neutralized the serum to test with all the antigens. Of the less active antigens, only those closely related neutralized to test with the very active antigen. For example, the serum Ad. gave very active transfer reactions with horse epithelium (to which the patient was clinically most sensitive) and also reacted with cow, dog, and cat danders and low ragweed pollen. Mixture of the serum with an equal volume of diluted horse epithelium extract (100 units per cubic centimeter) neutralized the reaction to all of these antigens (Protocols 4, 6, 8, and 23). Mixture with cow epithelium (5,000 units per cubic centimeter) neutralized the reaction to horse epithelium, but dog and cat danders and ragweed pollen did not noticeably affect the reaction with horse epithelium.

When the serum gave almost equally active passive transfer reaction to both antigens, cross-neutralization occurred only between closely related antigens and was of the reciprocal type. This is shown in Protocol 3 between dog and cat danders, and Protocol 4, between horse and cow danders. Between less closely related animals, such as horse and dog, reciprocal cross reactions were not observed and neutralization was specific unless one antigen reacted with the serum much more strongly than the other. Among the pollens, reciprocal cross-neutralization is known to occur between giant and low ragweed,[11] and between the various grasses.[10] Between the less closely related pollens, such as timothy and low ragweed neutralization was specific when the patient was equally sensitive, and the serum equally reactive to both. It is probable that more cross reactions might have been elicited if the antigen extracts were used in higher concentrations. The concentration used in the present work covered the range in which direct or specific neutralization ordinarily occurs with moderately sensitive serums.

It is apparent that the cross-neutralization reactions obtained depended on the serum tested and did not represent a constant relationship between the antigens. For example, Protocols 5, 6, and 7 showed neutralization of horse dander by dog, dog by horse, or entire absence of cross reactions, according to whether serum Am., Ad., or Je. was used for the test. When one antigen is said to be more active and to neutralize to test with another, the statement must be made with reference to some particular serum. With another serum the relationship may be reversed, depending upon the relative activity of passive transfer reactions of the serum to the two antigens. Piness and Miller[4] pointed out that cross-neutralization reactions between grass pollens were not the same in all of the serums used.

It was frequently noted that mixtures of serum with an antigen to which the serum was very reactive were neutral to test with a less active antigen but not on test with the antigen used in the mixture. Mixtures made with higher concentrations of the same antigen were

neutral to test with both antigens. In other words cross-neutralization occurred more readily and at a lower concentration than direct neutralization. For example, mixture with 100 units of dog dander extract rendered serum Am. neutral to test with cat dander, but not to test with the same strength of dog dander (Protocol 1). The mixture made with 1,000 units was neutral on test with either antigen. Similar cases are illustrated in Protocols 5, 6, 8, 13, 15, 17, and 21.

The amount of antigen required to neutralize a serum was not proportional to the amount of antibody, as measured by the dilution tests. On the contrary, as has been pointed out, the antigens to which the serum was very reactive and for which the dilution test showed a large amount of antibody, usually neutralized at lower concentrations than less active antigens. The activity of an antigen in neutralizing serum at least roughly paralleled its reaction in passive transfer sites made with the serum, which in general corresponded to the clinical sensitivity of the patient. In this respect the reaction is analogous to the absorption of antibody by bacterial antigens.

DISCUSSION

Although the cross-neutralizations in general were definite and readily reproducible, interpretation of the results in terms of reagins or specific antibodies presents more difficulty.

When one antigen neutralizes serum to test with another, the skin site is not refractory. In some cases, as has just been pointed out, it may still react with the antigen used for neutralization.

It seems impossible to avoid the conclusion that in cross-neutralization, the same antibody reacts with more than one antigen. This is not surprising in the case of closely related substances such as cat and dog danders. However, when the same antibody appears to react with such diverse antigens as horse dander and ragweed pollen (Protocol 23) or *Alternaria* and ragweed (Protocol 24) one may doubt the classical ideas of the specificity of the skin sensitizing antibody of the naturally sensitive man. These experiments suggest that passive transfer reactions to several antigens may be mediated by the same antibody. A slightly different interpretation has been suggested by Harkavy and Witebsky.[15]

The statement that a serum contains reagins or skin sensitizing antibodies for various antigens is really only a way of stating that it gives a Prausnitz-Küstner reaction with these antigens. In the absence of a method of physically separating the various antibodies, it is not possible to prove whether the different reactions are due to distinct protein molecules, to different radicals attached to the same molecule, or to the same radical. The idea that the serum of a patient with multiple sensitivities contains many independent reagins is based more upon analogy to artificially produced antibodies, than upon direct evidence. The cross neutralization reactions suggest that such a conception is erroneous.

In cross reactions also the naturally occurring skin sensitizing antibodies are less specific than artificially produced antibodies. Although, as pointed out by Hooker[17] there are qualitative differences in antibodies stimulated by homogenous antigen, the artificially induced antibodies are almost constant in their reactions. For example, the precipitin produced by injection of a foreign serum is relatively uniform in its cross reaction with serums of related species. On the other hand, the skin sensitizing antibodies occurring in the serums of patients sensitive to the same antigen vary greatly in their cross-neutralization reactions with other antigens. For example, the skin sensitizing antibodies for dog in the serums Am., Fi., Pa., Ad., and Je. vary so widely in their cross reactions with cat and horse epithelia that it would be impossible to describe them as a single specific antibody.

One may well question how many of the "weak" reactions of serums to various antigens, which are easily neutralized by more active antigens, represent real sensitivities. In the cases of timothy and ragweed pollens, it has already been pointed out that some of the reactions were not related to definite clinical symptoms. On the other hand, some of the most typical "weak" reactions have been correlated with a positive history. The patient Ad. whose reactions to dog dander and ragweed were readily neutralized by horse epithelium (Protocols 6 and 23), had mild but definite late hay fever, and prompt nasal symptoms on handling a dog. The patient St., a laboratory worker, who showed a weak reaction to *Iva* pollen, had definite symptoms on handling the pollen. Since the history of clinical sensitivity depends so greatly on the intensity of exposure to the antigen and on the acuity of observation by the patient, a sharp distinction between true and false reactions is often impossible.

The antigens used in the present investigation were the ordinary extracts used for testing and treatment in the clinic. It is known that many of these solutions contain a number of proteins of slightly different specificity. The possibility might be raised that cross reactions between the various extracts were due to the presence of common protein factors. Our present knowledge does not permit a definite answer to this in all cases. Studies of the antigenic proteins of timothy and ragweed pollens make it seem highly improbable.

It should be emphasized that the serums used in this work were all from hitherto untreated cases. The differences in the concentrations of various antigens neutralizing a serum are not to be confused with the differences in amount of the same antigen required to neutralize serum taken before and after treatment by injection of antigens.[18]

The use of the neutralization reaction to prove the identity of allergens, being based on a misconception of the specificity of the antibodies involved, is subject to many difficulties and possibilities of error. Most observers have based their conclusions on the use of a single serum with concentrated antigen extracts, and have accepted unilateral cross-

neutralizations as evidence of close relationship between antigens. Each of these conditions introduces the possibility of misleading results. However, when several serums are tested, using diluted antigen extracts on a quantitative basis, and only reciprocal reactions accepted as valid evidence, it seems probable that cross-neutralization may still offer a valuable method of studying the relationships of antigens.

CONCLUSIONS

1. Neutralization by one antigen of the passive transfer to another antigen is very frequent.

2. Antigens which react strongly with a serum tend to neutralize the reactions to antigens reacting less actively.

3. Reciprocal cross-neutralization occurs only between closely related antigens.

4. The cross-neutralization reactions vary greatly with the serum used for test.

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STUDIES IN EXPERIMENTAL HYPERSENSITIVENESS IN THE RHESUS MONKEY*†

V. The Technique for Demonstrating the Absorption of Undigested Protein

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IN 1927, one of the authors (M. W.) published a direct method for demonstrating, in human beings, the absorption of unaltered protein from the digestive tract.[1] The technique was a modification of the Prausnitz-Küstner phenomenon, by which specific excitation of a passively sensitized cutaneous site was induced by oral administration of the related antigen instead of by its local intracutaneous injection in the form of a sterile extract. As a result of the many investigations in which this technique has been employed, it is now generally admitted that the passage of detectable amounts of unaltered protein from the alimentary tract into the circulation is a physiologic phenomenon in most normal individuals.

The above technique was applied only in investigations on human beings as no experimental animal had been found which would regularly accept passive local sensitization with human reaginic serums. Under the circumstances, the scope of these studies was limited.

When it was recently discovered by one of us (H. S.),[2] however, that the skin of the *Macacus Rhesus* monkey could be passively and locally sensitized with human reaginic serums with a great degree of regularity, the possibility of applying the absorption technique in this animal presented itself. Investigation proved the same procedure which so successfully demonstrated the absorption of unaltered protein in human beings to be equally effective in the *Macacus Rhesus* monkey. The experiments performed in these studies will be briefly presented.

EXPERIMENTAL TECHNIQUE

The technique as it was applied in the monkeys was fundamentally the same as that employed in human beings. Its details are as follows:

A. *Sensitizing Serums.*—Three different reaginic human serums were employed for sensitization in the various experiments. The first was obtained from a child, Co., who suffered from asthma. By means

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of passive local sensitization studies on human skins, the presence of reagins for peanut and for cottonseed were demonstrated in this serum. The peanut reagin content of the serum titrated in the human skin by the serum dilution method of Coca and Grove[3] was 1:1024. The cottonseed reagin content of this serum was not titrated.

The second serum was supplied by a child, Mc., who suffered with severe asthma. Passive local sensitization of a normal human skin with this serum demonstrated the presence of cottonseed reagins. The titer of the cottonseed reagins was 1:1024.

The third serum was supplied by an adult, Pi., who had severe asthma. By passive transfer studies with this serum, employing normal human skins, the presence of cottonseed reagins in this serum also was demonstrated. The titer of these antibodies was 1:1024.

B. *Cutaneous Sensitization.*—This was accomplished by the intracutaneous injection of 0.05 c.c. of the undiluted human serum into a skin site of the monkey from which the hair had previously been removed by dry shaving. The injected point was then marked with an indelible pencil. The chest, abdomen, or thigh was the area in which sensitizations were usually performed.

C. *Testing for Absorption of the Antigen.*—1. The protein meal: For demonstrating the absorption of unaltered peanut antigen, a "peanut milk" was employed. This was prepared by mixing 10 gm. of crushed raw peanuts with 30 c.c. of water. In one instance the protein meal consisted of 10 raw peanuts. In the cottonseed experiments "cottonseed milk" was prepared by mixing 10 gm. of cottonseeds, from which the hulls had been removed, with 30 c.c. of water.

2. Administration of the protein meal: At least, from forty-eight to ninety-six hours were allowed to elapse between the cutaneous sensitization and the feeding of the antigen. The animal was deprived of all food for the twenty-four hours preceding the test. The antigen was administered by passing the peanut or cottonseed "milk" through a catheter, via the nose, into the stomach. In one instance the animal was allowed to eat the raw peanuts.

EXPERIMENTAL FINDINGS

Five tests were performed on four animals. Positive cutaneous reactions developed at the sensitized sites after all five feedings.

A. *The Positive Cutaneous Reaction.*—The reaction started with a blanching of the skin at and about the sensitized site and with an erection of the hair follicles, creating a "goose-skin" appearance. This was followed by the development of an irregular wheal with or without "pseudopods." No erythema surrounded these wheals as is the rule in human reactions of the same nature. Moreover, there seemed to be no pruritis associated with the wheal, as is usually the

case in human beings. The cutaneous reaction in the monkeys persisted for from four to six hours. It was limited to the sensitized area. (A more detailed description of the cutaneous reaction in the passively locally sensitized monkey has appeared in a previous communication).[2]

B. *Absorption Time.*—The interval which elapsed between the administration of the test meal and the onset of the cutaneous reaction at the sensitized site was considered the absorption time of that animal for that antigen. In Monkeys 36 and 193 which were fed by gavage, the absorption time for both peanut and cottonseed varied between five and ten minutes (Chart I). In Animal 28, which was allowed to ingest the raw peanuts the absorption time was not measured. In order to avoid excitement and to insure the normal consumption of the meal, this animal was allowed to stay unobserved in its cage while eating the peanuts. When examined at the end of one hour the fully developed reaction was already present. Animal 54 received his meal by gavage while under nembutal anesthesia. He received only one third of the usual amount of peanut milk. His absorption time was twelve minutes.

CHART I

THE ABSORPTION TIMES OF UNALTERED PEANUT AND COTTONSEED ANTIGENS IN THE RHESUS MONKEY

MONKEY NO.	SENSITIZATION		TESTING			
	HUMAN SERUM	SENSITIZING REAGINS	NO. OF DAYS AFTER SENSITIZATION	ANTIGEN MEAL	ROUTE OF ADMINISTRATION	REACTION TIME IN MINUTES
36	Co.	Peanut Cottonseed	2	10 Gm. of Peanut in 30 c.c. of Water	Through Nasal Catheter	5
193	Co.	Peanut Cottonseed	4	10 Gm. of Peanut in 30 c.c. of Water	Through Nasal Catheter	5
	Mc.	Cottonseed				0
36	Mc.	Cottonseed	4	10 Gm. of Cottonseed in 30 c.c. of Water	Through Nasal Catheter	8
	Co.	Peanut Cottonseed				10
28	Co.	Peanut Cottonseed	2	10 Raw Peanuts	By Ingestion	60*
54†	Pe.	Cottonseed	2	3.3 Gm. of Cottonseed in 10 c.c. of Water	Through Nasal Catheter	12

Sensitizing injection made with 0.05 c.c. of serum on thigh, abdomen, or chest.
*Not under observation during first hour.
†Animal under nembutal anaesthesia at time of meal.

DISCUSSION

The specificity of the reactions obtained in the *Macacus Rhesus* monkey with the use of human reaginic serums has already been discussed in an earlier communication.[2] Further corroboration of this principle is furnished in the present study. As illustrated in the case of Animal 193 (Chart I) which had been sensitized with two different human reaginic serums, both of which (Co. and Mc.) contained reagins for

cottonseed, but only one (Co.) reagins for peanut, the feeding of a peanut meal induced a reaction only at the site containing the related reagins (Co.). The nonreacting cottonseed serum (Mc.) did respond in another animal (No. 28) when the ingested meal consisted of cottonseed.

That the absorbed antigen is in its original unaltered form has been demonstrated in the many studies on human beings. This question was recently summarized by one of the authors (M. W.)[4] in a review of the literature on this subject.

The above experiments are significant for several reasons. First, they offer further convincing evidence that the skin of the *Macacus Rhesus* monkey can be passively locally sensitized with human reagin-bearing serums. Second, they confirm the findings, obtained in human beings, that detectable amounts of unaltered protein may enter the circulation from the gastrointestinal tract. Third, they show that the latter occurs with such a degree of regularity as to be considered a normal, physiologic phenomenon. Finally, the demonstration of this phenomenon in the *Macacus Rhesus* monkey has provided an experimental animal for those studies in absorption of unaltered protein which are not feasible in human beings.

SUMMARY

The same technique which has previously been employed in human beings to demonstrate the absorption of unaltered antigen from the gastrointestinal tract has been demonstrated to be equally as effective for use in the *Macacus Rhesus* monkey.

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SCARLET FEVER IMMUNIZATION BY INTRACUTANEOUS INJECTION OF SCARLATINAL STREPTOCOCCUS TOXIN*†

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IT IS a matter of common experience that *subcutaneous* injections of such substances as scarlatinal streptococcus toxin and alum-precipitated diphtheria toxin are at times followed by severe constitutional reactions. Especially in allergic individuals are such reactions likely to be more common and severe. Two years ago[1] we reported before this Association that in diphtheria prophylaxis such reactions could largely be avoided, and an immunity, as indicated by a negative Schick test, could nevertheless be achieved by giving the alum-precipitated toxoid *intracutaneously,* even though the dose was only one-tenth of the usual subcutaneous dose. At that time we called attention to the fact that this method of intracutaneous injection might be extended to other types of active immunization, notably scarlet fever. Today we wish to present our observations during the past two years on the intracutaneous injection of scarlatinal streptococcus toxin for the production of active immunity against scarlet fever.

Clinical Material.—Our test subjects included 140 children, all of whom had been found to have a positive Dick test. There were 61 boys and 79 girls. In age they ranged from sixteen months to thirteen years, a majority (95) being in the range of two to seven years, inclusively (Table I).

TABLE I

AGES OF 139 CHILDREN STUDIED

AGE	NO.
16-21 months	5
2 years	13
3 years	15
4 years	19
5 years	15
6 years	19
7 years	14
8 years	12
9 years	11
10 years	7
11 years	4
12 years	4
13 years	2
	140

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†Read before the Fifteenth Annual Meeting of the Association for the Study of Allergy, June 7, 1937, in Atlantic City, N. J.

Twenty-six of the children were frankly allergic, having been seen by us for an obviously allergic condition. The remaining 114 children gave no history of allergy.

Immunizing Material.—For immunization we used scarlatinal streptococcus toxin as prepared by a commercial house under license by the Dick scarlet fever commission, and packaged in 10 c.c. vials. The material was in the five strengths usually employed in subcutaneous injection, containing 500, 2,000, 8,000, 25,000, and 80,000 to 100,000 skin test doses, respectively, per cubic centimeter.

Method.—Each child was given weekly injections of toxin into the skin of the outer aspect of the upper arm. Injections were made quite superficial, in order to be sure that the toxin was really deposited in the skin. The quantity of fluid per injection in the earlier cases was only 0.05 c.c., but for the most part the amount was 0.1 c.c.

In our earlier observations, a Dick test, performed in the usual manner on the flexor surface of the forearm, was made six days after the second toxin injection and then six days after each subsequent injection. In our later cases the Dick testing was not begun until after the third, fourth, or fifth doses, and then continued after each or after every other toxin injection. Toxin injections were continued until the Dick test became negative, or until the child failed to return for further injections.

Dosage.—Our first consideration was the avoidance of severe and particularly of general reactions. It was planned, therefore, to begin with very small doses, and to increase the doses very cautiously and to give as many as should prove necessary to immunize. In our earlier cases, therefore, the dosage in terms of skin test doses was quite small, both as to the initial and the succeeding doses. Later, as we were emboldened by the lack of general reactions, the dosage was steadily increased.

In 117 children the initial dose was 25 STD* (0.05 c.c. of the weakest dilution), the other 23 receiving 50 STD at the first injection. Subsequent injections were either 50 or 200 STD and 800 STD, the latter dose being repeated until the Dick test became negative. In later cases a top dose of 2,500 STD was reached and repeated as needed. In others a top dose of 4,500 STD was employed, the successive doses being 50, 200, 800, 2,500, and 4,500 STD. The smallest total dosage which any child received was 275 STD, given in three injections (25, 50, 200 STD). The largest total dosage given to any child was 21,550 STD in 8 injections (50, 200, 800, 2,500, 4,500, 4,500, 4,500, 4,500).

Results.—A negative Dick test was achieved in 129 of the 140 children treated. Since a few children who after 3 doses were still Dick-positive, but did not continue treatment, we have figured percentage of results only on those cases receiving 4 or more doses: i.e., a nega-

*STD = Skin Test Doses.

tive test was obtained in 106 of 117 cases, or 90.6 per cent. It will be seen from Table II that no less than 23 children had a negative Dick test after only 3 doses, and 99 were rendered Dick-negative by 5 doses or less. In 30 instances 6 or more doses, with a maximum of 10 doses in 1 case, were required to get a negative test. In 123 children who were rendered Dick-negative the total number of skin test doses given was less than 10,000, and as low as 275 in 23 cases. Of the remaining 7 children, 5 received 10—12,000 STD, one 17,050, and one 21,550.

TABLE II

RESULTS OF INTRACUTANEOUS INJECTION OF SCARLATINAL TOXIN IN 138 CHILDREN

129 CASES RENDERED DICK NEGATIVE			11 CASES REMAINING DICK POSITIVE		
NO. OF CASES	NO. OF DOSES GIVEN TO EACH	TOTAL NO. STD GIVEN TO EACH	NO. OF CASES	NO. OF DOSES GIVEN TO EACH	TOTAL NO. STD GIVEN TO EACH
23	3	275			
1	4	300			
41	4	1,075			
8	4	3,550			
8	5	1,875			
9	5	3,575			
4	5	6,075			
5	5	8,050			
4	6	2,675	2	6	2,675; 3,475
1	6	4,375	2	6	6,075
4	6	6,075	2	6	8,550
1	6	8,550			
2	7	1,350; 4,575	1	7	3,475
1	7	4,625	1	7	4,175
2	7	5,175			
2	7	6,875; 8,575	2	7	8,575
2	7	11,050	1	7	10,275
1	7	17,050			
1	8	5,975			
4	8	7,675			
2	8	11,075; 21,550			
2	9	10,175; 11,075			
1	10	11,425			

The 11 children who did not become Dick-negative were given from 6 to 7 doses. The maximum dosage, however, in this group was under 9,000 STD in all but one case in which 10,275 STD were given. It is conceivable that some of these 11 might have been made Dick-negative had a larger dosage been given.

The ages of the 11 children not becoming Dick-negative were: 1, nineteen months; 1, two years; 1, three years; 2, four years; 4, five years; 1, seven years; and 1, ten years. It will be seen that the failures occurred largely in the younger age groups. Thus of 67 children aged five years or less, 9 did not become Dick-negative, whereas there were only 2 failures among 73 children aged six years or more. This is in accord with the usual experience with the subcutaneous method of procedure.

All the 26 allergic children became Dick-negative. It would appear that the allergic individual is certainly no less adequate in his immune responses than is the nonallergic.

Sex played no part in the results, 6 of the failures being in girls and 5 in boys.

Reactions.—The usual local reaction at the site of injection was an area of redness and swelling from 1 to 3 inches in diameter, very occasionally 4 or 5 inches and encircling the arm. The local reaction would reach its maximum in twenty-four to forty-eight hours and then rapidly subside, occasionally with a small central area of desquamation at the site of the injection. In no instance was there any disability as a result of the local reaction.

A general reaction was observed only twice in a total number of over 700 injections.

A girl aged five years was in error given as her fourth dose 2,500 STD instead of 800 STD. She developed fever that lasted twenty-four hours and reached a maximum of 100.6° F. There was a generalized erythematous rash, quite like that of scarlet fever in appearance and distribution, but lasting only forty-eight hours and without subsequent desquamation. Beyond rash and fever there were no complaints. A week later, the fifth injection (2,500 STD) produced no reaction. After 7 injections and a total of 10,275 STD she was still Dick-positive.

A boy of eight years, twenty-four hours after his third injection (800 STD) had a considerable local reaction and a suggestion of a scarlatinal rash on the abdomen. The next morning there was a generalized rash and a typical strawberry tongue. The following day the rash gradually faded. The maximum temperature reached was 99.8° F. on the second day. At no time did he complain of anything, was quite comfortable, active, and had no loss of appetite. There was no desquamation after the rash. The following dose (800 STD) at the regular interval caused no reaction, nor did the fifth, sixth, and seventh injections (2,500, 4,500 and 4,500 STD). The Dick test was still positive after the fifth dose, but became negative after the seventh.

In each of these cases the rash was so pronounced and so typical that the presence of scarlet fever was seriously considered. However the course, the lack of subsequent desquamation, and the absence of a sore throat settled the matter. In the one case in which the examination was made, there were no abnormal urinary findings. It is easy to understand that difficulties in differential diagnosis would arise in case of such reactions occurring in an immunizing campaign in the presence of scarlet fever among possible contacts.

Immunity.—We have as yet practically no first-hand information as to the degree of protection which these Dick-negative children possess. While no cases of scarlet fever have occurred among them, only three have actually been exposed to the disease so far as we know.

Duration of Immunity.—Our observations on the duration of the immunity, as far as they have gone, have been quite disappointing. Of 97 children rendered Dick-negative by a total dosage of 4,575 STD or less, 40 were retested six months or more afterward. Of these, 24 (60 per cent) were again Dick-positive, only 16 (40 per cent) remaining Dick-negative (Table III). Of the 29 children who had become Dick-negative after a dosage greater than 4,575 STD, none has as yet been rechecked.

TABLE III

RESULTS OF DICK TESTS SIX MONTHS OR LONGER AFTER INTRACUTANEOUS TOXIN INJECTIONS

TOTAL STD GIVEN	NO. OF CASES DICK-POSITIVE	NO. OF CASES DICK-NEGATIVE
275	10	6
300	-	1
1,075	8	6
1,350	1	--
1,875	4	1
2,675	1	1
4,575	--	1
Total	24 (60 per cent)	16 (40 per cent)

Among the retested group were 14 allergic children. To our surprise, their record was decidedly better than that of the others, 11 (78 per cent) remaining Dick-negative, and only 3 being again Dick-positive.

Boys, with 11 negatives and 9 positives, had a distinctly better record on retesting than the girls, of whom only 5 remained negative and 15 were again positive.

The resu'ts were poorer in the younger children. Of 23 children aged six years or less, only 6 were found Dick-negative on resting after six months or more; 17 were again positive. Of 17 children over the age of six years, 10 were still Dick-negative on resting and only 7 were positive.

Second Immunization.—Five of the children who had become Dick-positive after six months were again given intracutaneous injections of toxin. Four received 200, 800 and 2,500 STD successively a week apart and were then found to be Dick-negative. The fifth child required a fourth dose to achieve this result. In each instance the total dosage given in this second course of treatment was greater than that first given. Yet in no instance were the local reactions greater than those first experienced, and there was no general reaction.

Incidental Observations.—In the course of this study we noted certain things that are of interest.

We wish to call attention to the small number of allergic children in our series, in spite of the relatively large number of allergic children who come under our observation. This is due to the decidedly lower incidence of susceptibility (positive Dick test) among the allergic than

the nonallergic group. This might be due in part to the fact that not a few of our allergic children have at times been treated with sputum vaccines containing streptococci. But this is probably not the only reason. One of us (R. A. K.) has for some years been noting the occurrence of scarlet fever in the past medical history and has observed a distinctly lower percentage of allergics than nonallergics that have had this disease.

There appears to be a decided difference in the immunizing power of various lots of scarlatinal streptococcus toxin, even when obtained from the same source. For example, all of the 24 cases who became Dick-negative after only 3 injections and with a total dosage of only 275 or 300 STD were treated with the same lot of toxin. None of the other lots produced a negative test with this amount of treatment. This is in line with the observation of Friedman, Esserman, and Ginsburg,[2] who commented on the wide variations they found in the strength of toxin used for Dick testing, not only in different brands but even in the same brand with the same serial number, due apparently to the relative inaccuracy of present methods of standardization. They were even led to conclude that "the present scheme of active immunization against scarlet fever rests on an insecure foundation."

In the performance of the Dick test, particularly in those who had received toxin injections, we were impressed by the not infrequent occurrence of false positives. In such instances a control test performed with heated toxin at times gave quite as marked a reaction as did the unheated toxin. In recording our readings, however, we abided strictly by the original Dick technique which does not countenance such a control test. Otherwise, our results in the retested group would have appeared more favorable.

DISCUSSION

There is convincing evidence that active immunization against scarlet fever by the subcutaneous injection of full doses of scarlatinal streptococcus toxin (5 or 6 doses of successively 500, 2,000, 8,000, 25,000, and 80-100,000 STD) usually succeeds in conferring a satisfactory immunity. For example, Dick and Dick[3] report negative Dick tests in 95 per cent of 13,000 individuals so treated. Furthermore, the immunity conferred is adequate, in that among 12,584 susceptible persons so immunized in institutions where scarlet fever was epidemic, no case of scarlet fever developed.[3] Nor did any cases of scarlet fever occur among 3,000 susceptible nurses and internes, so immunized, on duty in hospitals for contagious diseases.[3] Moreover, the immunity so achieved is fairly lasting, in that 90 per cent of the Dicks' series were still negative when retested in from one to six years. The experiences of others are comparable to those cited. Nesbit and Thompson[4] in 171 persons tested five years after immunization found that 81 per

cent were still Dick-negative. Henry[5] found only 5 positives among 159 persons retested after a year. Bacon[6] found 78 per cent still negative after three years.

Why, then, should there be any attempts to modify or change this procedure? The answer lies in the high incidence of severe, even if not dangerous, reactions. Dick and Dick[7] in their first report mentioned the nausea, vomiting, fever, malaise, and rash experienced by all 5 of their earliest cases. In 1929,[8] they reported a 10 per cent incidence of general reactions among 12,775 persons immunized. Anderson[9] in reviewing this subject comments on the "Surprising unanimity of opinion as to the severity of reactions" which occur in 10 per cent to 15 per cent of individuals. These reactions have undoubtedly been the chief factor in preventing a more general adoption of the method of public health authorities as a general health measure.

It is an established fact that the skin plays an important part in the production of immune substances. That the intracutaneous injection of a given quantity of antigen will evoke the production of immune substances in amounts that would require a much larger subcutaneous or intravenous dose to call forth, was shown by Tuft[10] in case of typhoid vaccine and confirmed by us[1] in diphtheria prophylaxis. Moreover, it was our experience that systemic reactions were less common and less severe after intracutaneous injections. It, therefore, seemed logical to apply the method to scarlet fever prophylaxis.

That the Dick test can be made negative in over 90 per cent of susceptibles by at times even small doses intracutaneously, our work would seem to show. This confirms the observations of Robinson[11] who, over a year after our work had begun, reported the reversal of the Dick test in 24 subjects by 5 or 6 intracutaneous injections of totals of 7,150 to 10,750 STD.

That this can be accomplished almost without any general reactions is highly significant. An incidence of only 2 general reactions, neither very severe, in over 700 injections was far better than we had anticipated. Nor did Robinson encounter any general reactions in his 24 patients and 124 injections.

But does not the whole procedure fall down because of the failure to achieve a more lasting immunity? We think not. We are convinced that our earlier doses were decidedly too small. This is in keeping with the experience with the subcutaneous method. For example, Park and Schroder[12] got negative Dick tests with as few as 3 doses totalling 1,500 STD, but even after 1,200 STD the immunity did not last beyond six months. Yet 40 per cent of our cases did remain Dick-negative beyond six months, even though all but 3 had received less than 200 STD by the intracutaneous route. We are more than hopeful that a larger intracutaneous dosage (3 or more doses of successively 50, 200, 800, 2,500, and 4,500 STD, totalling at least 8,000 STD) than

that used in our earlier cases will give a much more lasting immunity. Especially in our allergic patients are we distinctly encouraged with their 78 per cent negative reactions after six months.

It is also significant that a second shorter series of injections in our 5 cases so retreated again established a negative Dick reaction. Would it, therefore, not be a logical and a practical procedure to retest these children twice a year, say in September and again in February, and then give another series of 4 or 5 injections to each Dick-positive child? It is certainly far less than we impose each year on our patients with hay fever. To be sure, it is quite obvious that such a procedure might not be practical as a general health measure because of inadequate cooperation on the part of too large a percentage of the general population. It might even be considered an unwise measure because it might engender an unwarranted feeling of safety in such noncooperative individuals. But as a measure to be applied in private practice among intelligent people it would at least seem worthy of trial. And that is our present intention. Perhaps at a later date we can report on this phase of the problem.

SUMMARY AND CONCLUSIONS

1. The intracutaneous injection of scarlatinal streptococcus toxin in about one-tenth the dosage employed subcutaneously will result in a negative Dick test in over 90 per cent of susceptibles.

2. Since the immunity so conferred would appear not to be as lasting as that by the full subcutaneous dosage, those immunized by this intracutaneous method should be retested every six months and if found Dick-positive should again receive a course of injections.

3. The intracutaneous method has the great advantage of unusual freedom from severe general reactions.

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DISCUSSION

DR. LOUIS TUFT, Philadelphia.—The results of the experiments just reported substantiate again the importance of the skin in immunity and emphasize the possible utilization of this organ in active immunization. This was demonstrated in experiments reported some years ago, in which we compared the antibody response following various routes of administration and found that the antibody response following intracutaneous injection, at least for typhoid vaccine, was much better than after the subcutaneous, intramuscular, or oral routes. These observations formed the basis for the intradermal method of inducing active immunization with typhoid vaccine. The results of these attempts indicated the usefulness of this method since, although local reactions occurred, general reactions were very infrequent. It was these observations, I believe, that led Dr. Kern later to try the intradermal method with diphtheria toxoid and now with scarlet fever toxin. As part of the work in our clinic at Temple University, my associate, Dr. Wenger, and myself have frequent occasion to immunize medical students and nurses against diphtheria and scarlet fever. Some of the reactions which occurred in these individuals were quite severe, being more so in adults than in children. We have minimized these reactions to some extent by including with each dose 0.1 or 0.2 c.c. of adrenalin (1-1,000). Although this reduces the tendency to reaction, it does not eliminate it completely. In some unpublished experiments (and this may have some bearing on Dr. Feinberg's paper of this morning), I found that adrenalin included with diphtheria toxin and administered to guinea pigs delays apparently the fatal issue produced by diphtheria toxin, without interfering with its antigenic properties. Although this indicates that adrenalin can be given with agents of this type without interfering with their immunologic properties, nevertheless, if such reactions can be avoided by intracutaneous administration, this procedure would seem unnecessary.

One thing that Dr. Kern and his associates have brought out has been the fact that reactions do not occur any more often in allergic individuals than in nonallergics. This merely adds emphasis to the growing belief that except for his specific sensitivity, the allergic individual is no different from the normal and that he does not become any more easily sensitized to other allergens nor does he react to immunizing agents any more intensely than the normal or nonallergic individual.

Finally, I would like to ask Dr. Kern or Dr. Crump whether they have used a control in doing the Dick test. The Dicks and others have previously stated that a control is unnecessary for the simple reason that in preparing the Dick test material, there is such a marked dilution of the streptococcus toxin that there is little chance of any nonspecific reaction occurring from the bacterial content. Nevertheless, I have found in a few instances that treatment has resulted in nonspecific sensitization to the bacterial protein, and that this can be detected by the use of a heated control. In my own practice, therefore, I use such a control following the administration of the pre-

scribed treatment. I wonder whether this might account for some of the positive reactions which were found to occur at the end of six months or later in the reported experiments.

Dr. Samuel M. Feinberg, Chicago.—As I understand the conclusions of the paper, a fractional dose of this toxin, about 10 per cent dose, will prevent a constitutional reaction as against a full dose of subcutaneous injection. On the other hand, it will not immunize as well as a full dose of the subcutaneous material.

I am inclined to believe from some of the work reported this morning that if one used a full dose intracutaneously, one would have even more systemic reactions than with the subcutaneous method. The question, of course, will have to be settled as to where the midpoint lies which will have the minimum of systemic reactions with a comparable amount of immunization. I think dose for dose, from our work, intracutaneous injections are more dangerous than subcutaneous.

Dr. Arthur F. Coca, Pearl River, N. Y.—I just want to ask if it has been thought feasible to initiate the immunization by intracutaneous injections and after a preliminary immunity has been established then to go over to the subcutaneous. I think we all agree that the reactions are usually noted after the earlier injections. We would then have the great advantage of the intracutaneous method in reducing the number of reactions and at the same time the obvious advantage of the larger doses of the subcutaneous in establishing a more permanent immunity.

Dr. Bret Ratner, New York.—Since Dr. Tuft's work on the use of the intracutaneous method for the immunization against typhoid came out, I have used it exclusively in my practice. I certainly recommend it to all of you, for reactions are mild and in most instances absent.

Another point I cannot refrain from mentioning is that Dr. Tuft remarked that as time goes on there seems to be a lesser and lesser difference between the allergic and the nonallergic, constitutionally. I think time will prove that an allergic individual acquires his condition as any other normal individual can under certain circumstances.

I would like to ask Dr. Crump if she has worked with children under one year of age. I noticed on her chart that she had but five children under two years of age. I have used this method of immunization against scarlet fever for many years, exclusively in children under one year of age, and I do not get any constitutional reactions. Dr. Hill of Boston told me that he had injected quite large amounts of typhoid vaccine in children several months of age and never saw a constitutional reaction.

Dr. Kern.—The performance of a tonsillectomy is followed in a certain percentage of cases by lung abscess. That was purely an abstract question to me until I had to have my tonsils out. Then I became very much interested in the incidence of this event by different methods of tonsillectomy and reached the conclusion that done under local anesthesia there was a lesser chance, and that is the way I had my tonsils out.

The question of reactions after these immunization procedures in children was purely an academic one until my two youngsters came along, requiring diphtheria and scarlet fever prophylaxis, one of them

being violently asthmatic. That is what started me on this train of thought, especially since I had seen some pretty violent reactions following the use of particularly the scarlatinal toxin.

The reduction of the severity of the reaction by the injection of adrenalin, as Dr. Tuft points out, can often be effected but does not by any means abolish the occurrence of reactions. So that in that regard we think that the intracutaneous injection method has a surprisingly good record.

He asked the question as to the performance of a control Dick test. Time was a bit short for getting this paper across, so that paragraph was omitted.

In the performance of the Dick test, particularly in those who had received toxin injections, we were impressed by the not infrequent occurrence of false positives. In such instances, a control test performed with heated toxin at times gave quite as marked reaction as did the unheated toxin.

In recording our findings, however, we abided strictly by the original Dick technique which does not countenance a control test. Otherwise, our results in the retested group would have appeared somewhat more favorable.

Dr. Feinberg's discussion needs no particular comment. We agree exactly with what he has said.

Dr. Coca's point about following up initial intracutaneous injections by later subcutaneous ones I think is an excellent one. It may well be that the reactivity of the more serious type can first be abolished by intracutaneous injections and then a more lasting degree of immunity achieved by the later subcutaneous injections.

In reply to Dr. Ratner, we had no children in our group under one year of age. There were only four under two, ranging from sixteen to twenty-one months.

ACQUIRED SPECIFIC HYPERSENSITIVITY TO SIMPLE CHEMICALS

I. Eczematous Sensitivity to Clothing and to Cosmetics; With Special Reference to Dyes*†

Joseph Goodman, M.D., Boston, Mass., and
Marion Sulzberger, M.D., New York City

THIS report deals with a group of cases representing certain selected types of allergic eczematous or "contact" sensitivity. As is well known, this form of hypersensitivity is usually confined to the skin and is characterized by the histologic findings of spongiosis or intraepidermal vesicle formation. The contact type of allergic sensitivity is usually directed toward nonprotein substances, toward so-called simple chemicals. As far as is known today, there is no tendency toward familial occurrence of this type of hypersensitivity and no association with asthma, hay fever, rhinitis, or any form of infantile eczema. In these and other ways, allergic eczematous contact dermatitis differs from atopic dermatitis and from atopic allergies in general.[1] Since the "contact" variety of sensitization dermatitis shows no particular tendency to be associated with asthma and hay fever, it is a form of allergy much more frequently encountered by dermatologists than by allergists. We believe, however, that today a knowledge of this form of skin sensitivity is important, both to the allergist and to the general practitioner, if only for the sake of the necessary considerations of differential diagnosis.

The present report is limited to certain selected forms of contact dermatitis. These specific forms are here selected and grouped because, in all of them, the causal agents are seemingly innocuous articles encountered in the everyday exposures of normal persons, regardless of occupation or avocation. It is true that the literature contains reports of contact dermatitis caused by these particular everyday agents; but these reports are sparse and scattered and, with few exceptions, deal with isolated cases. (One notable exception is found in a series of 14 cases of dress dermatitis reported by Bonnevie and Genner.[2]) Since the eruptions referred to are of such relatively common occurrence in our material, it seems that this subject merits further consideration.

It is, therefore, the object of this communication to call attention to the relative frequency of dermatitis eczematosa due to exposures to certain articles of clothing and to cosmetics; and to submit studies on a series of cases shown to be due to such exposures.

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†Read before fifteenth Annual Meeting of the Association for the Study of Allergy, Atlantic City, N. J., June 8, 1937.

DRESS DERMATITIS

This form of eruption occurs in women. We have found its occurrence to be so common that it may be concluded that many such cases are surely being seen in almost all types of medical practice. In the last two years, in our office and in our clinic practice, we have encountered 25 proved cases of dress dermatitis and numerous other cases in which the history and clinical picture permitted this presumptive diagnosis.

Not all of these cases could be studied as thoroughly as we should have desired and not all permitted satisfactory follow-up. However, the 25 cases here reported are all of proved etiology. Inclusion of other suspected cases, in which there was no opportunity for patch test investigation, might well have doubled the number in this series.

As a rule, this form of allergic dermatitis presents a fairly characteristic picture, conforming to that recently described by Bonnevie and Genner.[2] For this reason, we shall here present the history and description of only one representative case.

CASE REPORT

S. G., a forty-six-year-old, white obese, Jewish woman, was first seen on December 5, 1935. She complained of attacks of an itching eruption which had recurred at irregular intervals during the previous six months. There was no familial or personal history of other manifest allergic diseases, and no history of previous skin disease. Her general health was good, except for hyperidrosis and symptoms of the menopause, antedating the appearance of the eruption.

At the time of first examination, the patient presented an erythematous, papular, scaly, and in part vesicular eruption. This eruption was most marked in the periaxillary areas, the flexor surface of the arms, the upper chest, the anterior surfaces of the breasts, the upper back, and the neck. On the abdomen, on the lower back, and on the buttocks, as well as on the lower portion of the face, there was less severe involvement. The hands, feet, and legs were entirely free. Noteworthy findings were the sparing of the pit of the axillae, and the high degree of involvement of the periphery of the axillae and of the periaxillary folds, which showed acute vesiculation, weeping, and crusting. The folds under the breasts were entirely spared. The eruption was not sharply demarcated in any area; the erythema was bright red, and there was little lichenification or pigmentation. The itching was intense, but there were no visible scratch marks.

On questioning the patient, it became clear that the eruption had first appeared about six months previously, shortly after the purchase of a new, dark blue silk dress. This dress had been purchased about one month before the onset of the eruption. The patient recalled wearing this particular dress the day preceding, and the day of the first attack. It is noteworthy that the patient suspected this dress so little that she was wearing it when she was first seen by us.

The patch test with this silk dress gave a papular and erythematous reaction (2-plus). The patch test with paraphenylendiamine (2 per cent in petrolatum) showed a questionable reaction, while the patch test with silk protein was negative.

As soon as the patient was convinced of the possible causal rôle of dresses, she volunteered her suspicions of a second dress (black wool). Patch test with material from this dress showed a papular, erythematous, and edematous reaction.

Local x-ray and topical applications, plus the elimination of the two above mentioned dresses, were followed by rapid relief from itching, and disappearance of the dermatitis within about two weeks. The patient then remained well for an interval of nine months, with the exception of one occasion, when itching recurred after she deliberately wore one of the incriminated dresses "to see what would happen." However, on September 21, 1936, she returned with a new eruption similar to, but less extensive than, the first. At the time of this examination, the patient presented palm-sized, fairly sharply circumscribed areas of erythema and edema of the periaxillary folds, the antecubital spaces, and the upper portion of the chest. There were a few erythematous papules on the upper arms. The pit of each axilla was again spared.

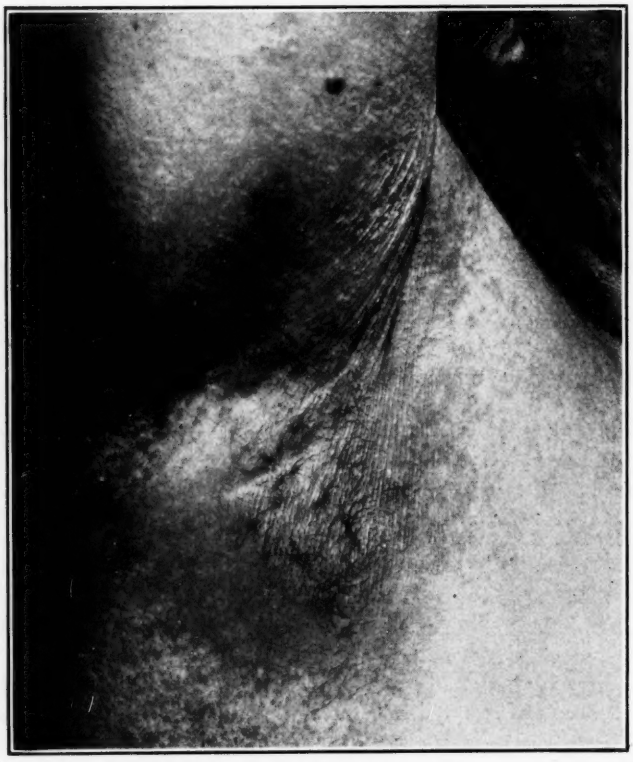

Fig. 1.—Dress dermatitis of axilla; note sparing of the axillary pit.

Five days before this visit, the patient had put on a new green crepe dress for the first time. This dress was worn for only three hours. That evening, itching commenced. By the next morning there was severe itching and a mild recurrence of the dermatitis. Patch tests with the green crepe elicited a 2-plus reaction. The dermatitis responded rapidly to topical remedies; the offending dress was discarded; and the patient has remained well. (Period of observation since last attack: fifteen months.)

The case just reviewed illustrates certain points which were of common occurrence in our series.

As already stated, the report of Bonnevie and Genner[2] stresses the characteristic features of dress dermatitis. We, too, have found the

picture of this dermatitis so uniform that, in most instances, inspection alone suggests the etiologic factor. In only one important respect do our findings differ from those of Bonnevie and Genner: while these authors found that all of their cases were caused by blue clothing, in our series many different colors have been proved to be responsible (see below).

By assembling the more constant features in our 25 female patients with dress dermatitis, we have been able to construct a composite and

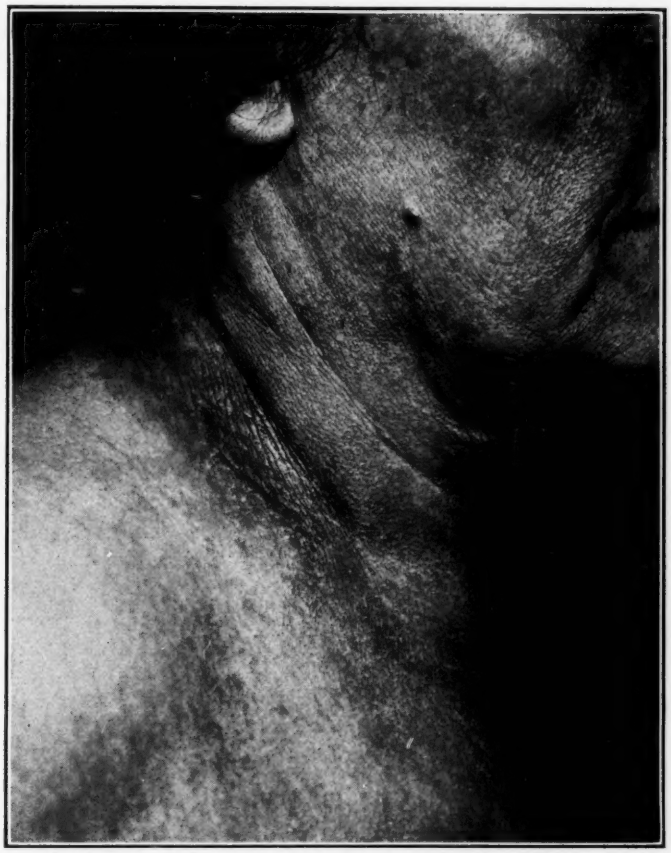

Fig. 2.—Dress dermatitis; note the more severe involvement of the site of friction with the dress collar.

fairly characteristic picture. The average age was forty-three years—the youngest patient being nineteen years and the oldest 61 years. Since 18 of our 25 cases were in the age group between forty and sixty years of age, there seems to be a tendency for this variety of dermatitis to affect middle-aged women. Whether or not this tendency is based upon some relationship to the climacteric, must be the object of further study. In this connection it must be mentioned that the amount and type of perspiration, as well as obesity, have been mentioned by

Bonnevie and Genner[2] as playing a rôle in the production of dress dermatitis; and both obesity and axillary hyperidrosis are more likely to occur in middle-aged women. In our series also, most of the patients were overweight, and the majority suffered from hyperidrosis, particularly of the axillae. In addition, it seems possible that, at least in some instances, the use of depilatories and deodorants, or the trauma of shaving may have acted as contributory factors in producing the sensitization.

Characteristically, dress dermatitis affects the axillary and periaxillary regions but spares the pit (Fig. 1). This sparing of the pit is of considerable importance in differential diagnosis, since this site does

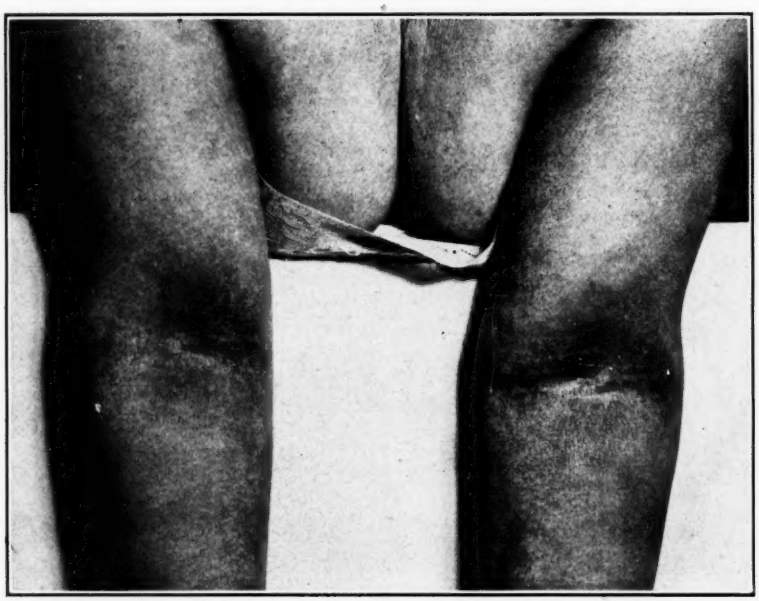

Fig. 3.—Dress dermatitis; illustrating the antecubital involvement and the obesity of the patient.

not usually remain unaffected in moniliasis, in seborrheic dermatitis, and in psoriasis of the axillary regions.

The antecubital spaces and the sides of the neck, where the dress touches and rubs, are also usually involved by the dress dermatitis (Figs. 2 and 3). In the more severe cases, the eruption also includes the intervening areas, so that the entire upper portions of the body may become affected (flexor surfaces of arms, sides of face, chest, breasts, back, upper abdomen, etc.). In some instances, there is even greater tendency to generalization—the extensor surfaces of the arms, the thighs, buttocks, and entire face being involved. In none of our cases did the eruption spread to the hands, feet, and lower legs.

The distribution varies slightly from case to case, depending on the cut of the dress and on other factors, such as the amount of protection offered by undergarments. Not infrequently, we have observed a fairly sharp line of demarcation on the chest; the dermatitis descending only to the upper edge of the undergarments.

Even in the generalized cases the axillae and the antecubital spaces are the areas of most severe involvement. This predilection for axillae and antecubital areas suggests that there is urgent need of further studies of the pH of the sweat in its relationship to this type of dermatitis (alkalinity?).

The character of the dermatitis is that of contact eczema in general, with varying degrees of edema, erythema, papulation, vesiculation, weeping, crusting, and scaling. In our cases we have never observed the pigmented, thickened, lichenified areas or the large excoriated papules of atopic dermatitis. In spite of the intense itching, no visible scratch marks are seen. In several of our cases, as was also noted by Bonnevie and Genner,[2] axillary sweat-gland abscesses, and furuncles supervened. *We believe that hypersensitivity to dress materials etc. may even play a part in the causation of certain cases of hidroadenitis appearing without manifest dress dermatitis.*

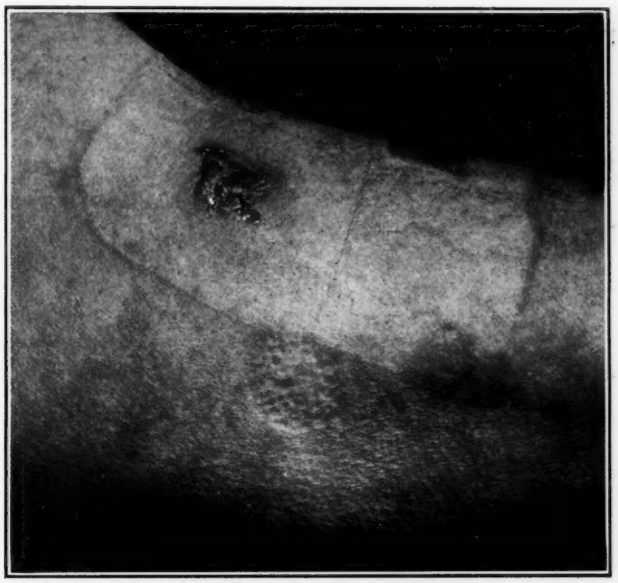

Fig. 4.—Bullous reaction to patch test with black silk dress material in a case of dress dermatitis.

As in the series of Bonnevie and Genner,[2] many of our cases presented a seborrheic scaling of the scalp. However, it is as yet undetermined whether there is any direct connection between the seborrheic state and dress dermatitis.

In all the 25 cases here reported, there were positive patch test reactions to dress materials. The reactions varied from case to case, ranging from a moderate degree of erythema to large bullae. In 19 of our 25 cases there was a high degree of hypersensitivity, the patch test reactions being vesiculobullous in character (Figs. 4 and 5).

As stated above, in our series the patch test reactions and the dermatitis were produced by materials of many different colors. This finding differs from that of Bonnevie and Genner,[2] in whose cases only blue materials were found responsible. In our cases, for example, there were 30 positive reactions to black materials, and 14 patients reacted to black materials only. (Not all of these 14 were tested with materials of other colors, because in many instances removal of the causal black dress sufficed to check the eruption and to prevent recurrences.) There

Fig. 5.—Vesiculobullous reactions to patch tests with red silk crepe and with black silk crepe in a case of dress dermatitis.

were 9 patch test reactions to brown materials; 8 to red materials; 6 to blue materials; 5 to green materials; and 2 to orange materials.

We were able to patch test 16 of our 25 patients with "pure" dyes.* Ten showed a positive reaction. Since we were unable to ascertain the actual dye used in the incriminated dresses, and since only a series of arbitrarily chosen dyes were used in our tests, it is quite possible that the 6 cases not reacting to our dye patch tests were, nevertheless, sensitive to some dye not among those used in testing. It seems more than likely that dyes are responsible for the majority of cases of dress dermatitis, but unfortunately our investigations thus far do not enable us to ascertain the relative likelihood with which certain types of dyes may cause dermatitis.

*Patch tests on large series of normal control individuals demonstrated that the commercial dyes produce no reaction in the nonhypersensitive, even when applied in highest possible concentrations.

Polyvalent sensitivity was not uncommon in our series. One patient reacted strongly to materials of 7 different shades and colors. This patient showed positive reactions to 13 of 20 colored dress materials applied as patch tests (Fig. 5).

Moreover, we have gained the impression that one and the same patient may exhibit a hypersensitivity to various chemically unrelated dyes. We could find no relationship between chemical composition and structure, and the varying and apparently haphazard association of hypersensitivities. It is obvious that this incomprehensible association of hypersensitivities makes it impossible to predict which colors or dyes will prove innocuous to the sensitive patient. Thus, some patients experience great difficulty in selecting dress materials which will not produce dermatitis. In some instances, it has been necessary to advise a patient to confine herself to the wearing of dresses made only from materials which observation had proved to be innocuous in her particular case. In other instances, patients have found it essential on each occasion to have patch tests performed with the actual dress materials before their purchase.

While the prophylaxis and prevention of recurrences are, therefore, in many instances extremely difficult, treatment of the dermatitis is relatively simple. The elimination of the offending articles of clothing, the application of soothing and antipruritic lotions, and, in severe cases, a few superficial roentgen-ray treatments usually suffice to terminate the attack within a period of several weeks. In some instances, however, several months may elapse from the time of the last exposure to the complete freedom from symptoms.

The majority of cases of eczematous dermatitis produced by hypersensitivity to dress materials conform to the above descriptions, and occur in women as a result of wearing dresses made with the offending material. There are, however, among our cases of dye-sensitivity, some due, not to the materials of dresses, but to other colored articles of clothing—for example, scarves, coats, children's jumpers, stockings, and socks. In these cases, of course, the localization is usually characteristically different from that of true dress dermatitis.

In still other cases, while dress materials produced the dermatitis, they did so as occupational hazards, rather than as articles of wearing apparel. We have recently seen 3 cases, in which the occupation seemed to play a rôle in producing the hypersensitivity. One case occurred in a female sewing-machine operator; one, in a male tailor; and one, in a male sewing-machine operator.

The female operator presented a severe, eczematous, scaly, erythematous eruption on the hands, forearms, and antecubital spaces. She herself had noted the exacerbations of this dermatitis after her occupational handling of certain materials, particularly of black materials.

Patch tests showed strong vesiculobullous reactions to 7 different black materials, and to 2 brown materials with which she had worked. Blue and green materials tested at the same time produced no reactions. This patient's patch test reaction to 2 per cent paraphenylendiamine in petrolatum was 4-plus (bullous). There was a history of the occurrence of a generalized eczematous dermatitis which resulted from the wearing of a brown dress two years before our first examination.

In the male sewing-machine operator, the dermatitis was present on the face, arms, hands, and popliteal spaces. This patient showed a 2-plus reaction to patch tests with a suspected red crepe material with which he had been working prior to the onset of the dermatitis. His reaction to paraphenylendiamine was 1-plus.

In the third case—that of the tailor—the occupational causation is by no means certain, for the localization of this patient's dermatitis corresponded to the typical distribution of clothing-dye dermatitis when due to wearing articles of male clothing (see below). So that, while the sensitization may or may not have been produced by occupational exposure, the presenting erythematous and vesicular dermatitis of the neck, etc., could be shown to be due, in all probability, to the wearing of a certain overcoat. The material of the suspected overcoat elicited a 2-plus patch test reaction.

We have observed other cases of nonindustrial clothing-dye dermatitis in males. These were in many ways similar to two cases previously reported in the literature: the first, by Simon and Rackemann;[3] the second, by Bonnevie and Genner.[2] In our 2 patients, both young men, the distribution of the eruption was characteristic and characteristically different from that observed in females with dress dermatitis. In each instance, the eruption started on the lower legs, and gradually spread upwards to the lower border of the short underdrawers. The popliteal spaces and posteromedial aspects of the thighs were involved; the extensor surfaces were relatively free. The lower border was at the upper shoe margin in one instance, but in the other, the dermatitis also involved the dorsa of the feet and toes. The eruption was not acute and not vesiculating; but was chronic, erythematous, scaly, and somewhat lichenified and infiltrated. The itching was severe. The neck at the site of contact with the coat collar, and the wrists at the site of contact with the coat sleeves, presented a dermatitis similar to that of the legs. The lines of demarcation of the involved areas were not sharp, but there was gradual transition to normal skin.

In one case our investigation was interrupted before tests and clinical elimination could be carried out. In the other case, one of over fifteen years' duration, the elimination of a brown suit and other clothing suspected to be the cause, plus mild topical applications and protection achieved by wearing cotton garments under the trousers resulted in a rapid cure (period of observation since cure: one year). In this case,

patch tests were performed with 41 dyes, including many used in dyeing clothing. Just as in the case reported by Simon and Rackemann,[3] there was a marked polyvalent sensitivity to dyes, 7 eliciting positive reactions. The dyes which produced the reactions were, for the most part, chemically apparently unrelated. It is noteworthy that this patient suffered from chronic *urticaria of long standing, which also disappeared after the cure of the dermatitis* under the above outlined measures. (See also below, the discussion of urticaria associated with lipstick hypersensitivity.)

In another case of clothing-dye dermatitis in a male, not a suit, but a new pair of red pajamas was found to be the cause of the eruption. In this instance, the dermatitis involved the face, trunk, and extremities. The patch test with unwashed and unboiled material from the pajamas elicited a 3-plus reaction. Nine days after the first patch test, a second patch test was applied with the washed and boiled pajama material. The reaction to the washed and boiled material, although still positive, was markedly less than to the first test.*

SHOE DERMATITIS

Dermatitis of the feet caused by shoes has been mentioned by previous observers. To our knowledge, the first mention in the American literature was that by Br. Bloch.[4] Subsequent reports have been submitted by Lewis,[5] Anderson and Ayres,[6] Sulzberger and Kerr,[1h] and Beerman.[7] Most of the earlier reports concerned themselves with cases which were acute in nature. Our observations on the other hand were made on shoe dermatitis of the subacute and chronic varieties.

While in the instance of dress dermatitis the differential diagnosis between seborrheic dermatitis, atopic dermatitis, and contact dermatitis of other etiology constitutes the principal consideration, shoe dermatitis (as pointed out by previous observers) requires differentiation mainly from the eczematous forms of dermatophytosis. All of the 5 cases here reported had been diagnosed previously as ringworm of the feet, and treatment for ringworm had been carried out for varying periods of years with little or no avail. The eruptions on the feet of these patients were eczematous, presenting various degrees of erythema, scaling, and vesiculation. In many respects they thus closely resembled eczematous ringworm. However, in every case certain characteristics led us to suspect that we were dealing with dermatitis due to contact excitants, rather than with ringworm. These distinguishing characteristics may be summarized as follows:

1. In 4 of our 5 cases there was little or no involvement of the interdigital spaces; and, particularly, little or no maceration.
2. The juxtaposed areas of the toes were not usually involved.

*We are indebted to Dr. I. Rosen for permission to include this case.

3. There was characteristic involvement of the dorsa of the toes, particularly of the great toes.

4. There was a maximum of the eruption at the sites of maximum pressure or friction from the shoes (the dorsal aspect of the foot distal to the upper margin of the low shoe, the area of the instep, the dorsal and lateral aspects of the little toes, the lateral and medial aspects of the heels, and the periphery of the soles) (Figs. 6, 7, and 8).

Fig. 6.—Shoe dermatitis; illustrating particularly the line of dermarcation at the upper shoe margin.

Fig. 7.—Shoe dermatitis; illustrating the predilection for areas of maximum pressure and friction.

5. There was a tendency for the eruption to be demarcated by the shoe margins (Fig. 6).

6. The procedures usually successful in treating dermatophytosis had proved unsatisfactory.

7. The itching was more severe than is usual in uncomplicated dermatophytosis.

In all of these cases, positive patch tests demonstrated hypersensitivity to one or more portions of the shoes which were being worn by the

patients. (Inner linings, brown and black uppers, and even brown and black shoe polishes were found responsible in some instances.) One patient gave positive reactions to 17 samples of leather removed from 4 different pairs of shoes. Four patients were sensitive only to brown leathers, while the fifth was sensitive both to black and to brown leathers. The patients sensitive only to brown leathers were, nevertheless, unable to wear black shoes because of the usual brown leather linings.

In most of our cases, it has been difficult to prevent recurrences, mainly because of three complicating factors: first, the practical difficulty of obtaining and continually wearing shoes made entirely of leathers which were proved to be innocuous; second, the accompanying hypersensitivities, such as to colored socks and to colored shoe polishes;

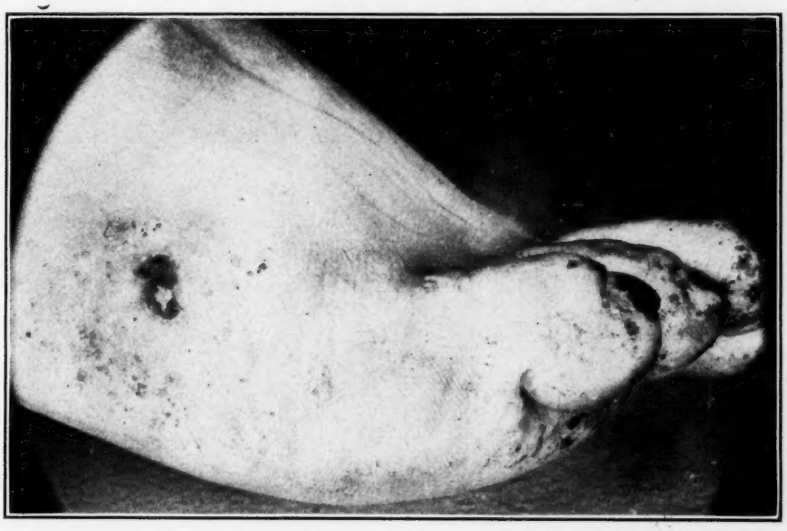

Fig. 8.—Shoe dermatitis; illustrating the tendency to affect the sides of foot, and the lateral and dorsal aspects of toes, with sparing of the juxtaposed skin surfaces. (The staining of the toenails and of the crusts is due to previous applications of potassium permanganate.)

third, the complicating presence of dermatophytosis which was apparent and active in one instance, and which may have preceded the development of the dye sensitivity in our other cases. In spite of these difficulties, 3 of our 5 patients have found and are now wearing shoes which produce no irritation. A fourth patient has improved materially since he has avoided tan shoes and tan shoe polishes. The fifth patient improved after discarding the offending shoes; and, according to our last information, has had no recurrences.

We wish to stress two particular considerations in regard to this variety of dermatitis of the feet. First, we have gained the impression that coexisting or preceding dermatophytosis and hyperidrosis were factors favoring the production of the sensitization, and that hyperi-

drosis and friction were important contributing factors in the production of the individual attacks or exacerbations of the eruption. Second, it is to be emphasized not only that this form of dermatitis must be differentiated from epidermophytosis, but that in order to find the cause, patch tests must be performed with all the substances which may in any way come into contact with the feet. These patch tests must, therefore, include shoe polishes, shoe uppers, all the materials of the linings and tongue, the shoe laces, inlays, sole leather, socks, slippers, sneakers, etc.

Fig. 9.—A case of sock dermatitis with sharp demarcation at the upper sock margin. Patch tests are in place on the outer aspects of the leg, on normal skin above the affected area.

Shoe dermatitis may occur alone, or may be associated with dermatitis from brown, black, or other colored socks. In frank cases of sock dermatitis, the offending substance may be either a dye or a finisher (sulfonated oil, etc.[8]). While in some instances sock dermatitis appears only in the areas covered by shoes (probably because of pressure, friction, and prevention of sweat evaporation), in other instances the dermatitis extends to the top of the sock. A case of the latter type, with a positive patch test reaction to a dye (paraphenylendiamine), is shown in Figs. 9 and 10.

DERMATITIS DUE TO COSMETICS

Dyes are encountered not only in wearing apparel but also in many other common environmental exposures, such as furniture, hangings, drapes, carpets, leather goods, etc. Cosmetics are another almost universal source of dye exposure, particularly among females. In discussing dyes in cosmetics, we do not refer particularly to the now well-known hair dyes, which in general contain paraphenylendiamine or related compounds. We wish, rather, to call attention to forms of cosmetic-dye dermatitis which, although previously described, are less well known. These include dermatitis of the contact type produced by the colors contained in powders, creams, lotions, dentifrices, rouges, and lipsticks.

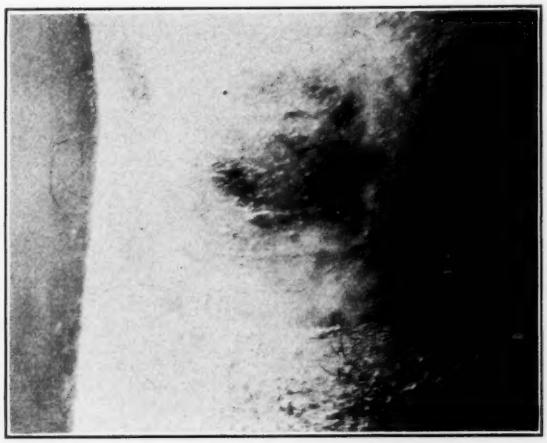

Fig. 10.—The same case as shown in Fig. 9, forty-eight hours later, showing the strongly positive reaction to patch test with 2 per cent paraphenylendiamine in petrolatum.

We have recently reported a series of 12 cases of irritations of the lips, and 2 of dermatitis of the face, caused by lipstick.[9] In all of these cases, it could be demonstrated that there was a sensitivity to coloring materials contained in the lipsticks. While indelible dyes of the bromfluorescein group were the most frequent causes of positive patch test reactions in this lipstick series, a large number of positive patch test reactions were also elicited by nonindelible lake colors, in particular by 1 sulpho β-naphthalene azo β-naphthalol. In the majority of our cases, our investigations permitted us to supply the patients with substitute lipsticks which could be used without causing recurrences of the irritation.

In these 14 patients, neither the fatty ingredients of the colorless lipstick base nor the perfume could be considered as important causes of the irritation. In none of our cases was there a demonstrable hyper-

sensitivity to methyl heptine carbonate, although Baer[10] had incriminated this common ingredient of perfume in his case of lipstick sensitivity.

In considering lipstick irritation, the possible rôle of eosin and flavine dyes in producing photosensitivity must be borne in mind (compare eruptions from sulfanilamide). It seems worthy to mention that one of our dye-sensitive lipstick patients suffered from chronic generalized urticaria while she used the offending lipstick, and that the urticaria disappeared, and remained absent after the elimination of the dye found to be responsible for the production of the irritation of the lips. As discussed above an analogous urticaria was encountered in one of our male patients with clothing dermatitis.

We have seen other cases of dermatitis probably due to the dyes in cosmetics, in which, however, we have not been able to carry out

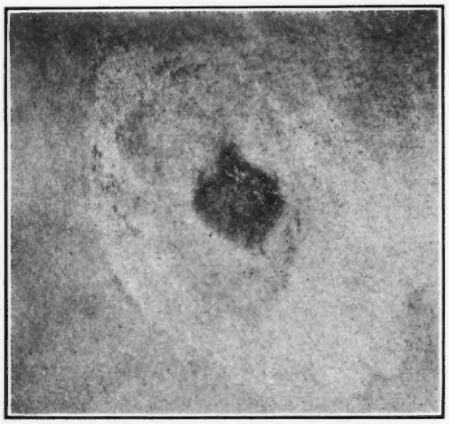

Fig. 11.—Positive patch test reaction to a red dress material. This patient had suffered not only from lipstick cheilitis but also from a dress dermatitis. Patch tests with lipstick also elicited positive responses.

investigations permitting the exact determination of the responsible constituents. In one case of nail polish dermatitis, an analysis by means of patch tests demonstrated that the solvent ethylene dichloride, and not a dye, was the responsible constituent. This case illustrates the necessity for the careful analysis of hypersensitivities by means of patch tests, and the danger of blaming any particular ingredient of a causal mixture without skin test verification.

Unfortunately, such analysis by patch tests cannot always be carried out. In some instances the relative simplicity of the substance and the cooperation of the manufacturer permit a complete study but in many other instances, such as in the case of shoe leathers (as pointed out by Beerman[7]), the substances are so complex that an accurate determination of the causal constituent is often impossible. In still other cases, jealously guarded secret formulae prevent the determination of the exact nature and composition of the compound or mixture concerned.

In closing, it may be mentioned that we have seen instances of the combination of sensitivity to lipstick and to red clothing materials (Fig. 11); of sensitivity to brown clothing, to brown shoe polishes and to brown shoe leather; of sensitivity to lipstick and to colored (rotogravure) newsprint reproductions, etc. When these combinations occur, they furnish further evidence that it is the dye constituent of each substance which is responsible for the dermatitis.

From the available evidence it may be concluded that dye sensitivity is based upon an allergic mechanism; and our observations indicate that this form of allergy is not uncommon. However, the incidence of dye sensitivity must be regarded as relatively low when one considers the enormous quantities of dyes used each year and the constant exposure to dyes from a variety of sources. Nevertheless, the cases reported here demonstrate the importance of bearing dye sensitivity in mind in the investigation of contact dermatitis.

It is also well to bear in mind that not only contact dermatitis, but also other types of allergy may be caused by dyes, perhaps through their acting as haptens in conjugation with larger (protein ?) molecules. It is, for example, well known that asthma, rhinitis, urticaria, prurigos, and dermatitis of atopic type may result from dye exposure. (For discussion of different forms of allergy, all produced by paraphenylendiamine, see, for example, R. L. Mayer.[11])

The use of synthetic dyes has today grown to such enormous proportions that the average individual is constantly exposed to great quantities of these potential allergens. A consideration of the many dyed fabrics which are present in the average home makes the assumption logical that dyed particles must be a part of ordinary house dust. The allergenic properties of these dyed particles may well be worth serious investigation in connection with the many unsolved questions regarding the nature and properties of varying "house dust allergens."

SUMMARY

Various types of eczematous contact dermatitis due to allergy to dyes are discussed.

The clinical course and appearance of dress dermatitis in the female are considered in detail. Twenty-five cases are reported, in which the dermatitis was proved to be due to dyed dress materials.

The results of patch test studies of these patients are reported. The polyvalence of sensitivity found in many of these cases, and the many difficulties encountered in the prophylaxis of dress dermatitis are discussed. Brief mention is made of the possible rôles of perspiration, friction, occupation, etc., in the production of the sensitivity and in the precipitation of the attacks.

The clinical course and the appearance of clothing dermatitis in the male are also discussed, and two pertinent cases are reported.

Other types of dye dermatitis are mentioned including dermatitis of the feet due to shoe leathers, which is discussed in the light of studies made on 5 patients.

Among the causes of dermatitis produced by cosmetics, dyes play a significant rôle. In illustration of this point reference is made to the authors' studies of 14 cases of lipstick sensitivity.

Attention is directed to the ubiquitous presence of dyes and dyed substances and of the possible importance of dyes or dye-conjugates in forms of allergy other than contact dermatitis.

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962 PARK AVENUE

DISCUSSION

DR. ARTHUR F. COCA, Pearl River, N. Y.—Dr. Piness pointed out yesterday that I should not have been asked to discuss this paper, and I am sure you all realize the truth of his criticism. It would be a mistake to detract attention from the practical interest of Dr. Sulzberger's paper by discussing the etiology or method of spread of this kind of allergy; and that is the only aspect of it in which I have really had any active interest.

I have been interested for some years in the treatment of contact dermatitis due to vegetable and animal oils by the procedure of desensitization by injection of the respective oils. I believe, although the question is not definitely settled, there are many cases that are relieved by this treatment. The treatment is indicated, of course, in those cases in which avoidance, which is the best form of handling such cases, is not possible. I would only ask Dr. Sulzberger whether he has some ideas about the application of this kind of treatment in cases of contact dermatitis due to water soluble excitants which are naturally more dangerous when injected than are the slowly absorbed vegetable-animal oils.

DR. FRANK A. SIMON, Louisville.—Dr. Sulzberger referred to the case of dye sensitivity which Dr. Rackemann and I reported a few years ago. As some of you know, I myself am the patient whose case we reported. I am very sensitive to azo-dyes; have been sensitive to azo-dyes for nearly nine years. I have contact eczema, as Dr. Sulzberger described, when I come in contact with dyed clothing or any sort of dyed material. I have had lesions on my feet from dyed shoes and from shoe strings in the shoes. I have had lesions on my neck from an overcoat collar or from a coat collar, such as I have on now. I have had them on my hands and wrists from the sleeves of the coat. I have had them on the forearm (medial aspect) from having my arm on a table in which the wood was stained with a dye.

Last summer I moved into a new house and the steps were stained with a red dye. I walked on those steps without shoes and stockings on, and all the skin on the bottom of my feet peeled off, that is, it did that after I had the acute contact eczema on my feet.

I have to test all the clothing I wear. I test the suits before I buy them. I test the lining, this lining and the lining in the pockets which may be different than the rest of the lining. I test the shoe strings and test my shoes before I wear them, and my ties. I test my wife's clothing, my children's clothing. I test the upholstered furniture in my home. I have to be careful of anything that I touch that is dyed.

As long as I keep away from these dyed materials, I am able to live a fairly normal life and get along without much trouble.

I have just a few lesions on my hands now. I am not absolutely certain that these are due to dyes, but I can produce on myself anywhere, any part of my body, any time I want an area of this contact eczema, just any size or shape I want, by applying a piece of dyed cloth to that area and leaving it on for twenty-four hours. I get patch tests like Dr. Sulzberger showed in which there are large vesicles and they itch a great deal. It is just exactly as Dr. Sulzberger described.

DR. WILLIAM W. DUKE, Kansas City, Mo.—Some time ago I saw a doctor who said he was sensitive to his wife. He was very much excited about the matter, very much agitated, because every time he would get in the room with his wife, he would have asthma and break out with itching.

He was very sensitive about it and would not let me test either him or his wife, so I surmised he might be sensitive to heat, but the fact is he might have been sensitive to his wife's clothes.

DR. HARRY S. BERNTON, Washington, D. C.—I desire to supplement Dr. Sulzberger's very instructive presentation with a brief report of a case which may possibly be of interest to you. The patient was a man

about thirty-five years of age, an architect by profession. He had a very extensive eczema restricted to his fingers. He was, moreover, subject to autumnal hay fever. A complete series of cutaneous tests was performed. The pollens of the short and giant ragweeds gave markedly positive reactions. These did not account for the eczema. Finally, we performed a series of patch tests as outlined by Dr. Sulzberger in one of his publications. A violent reaction ensued from the application of a solution of dichromate to the skin. I enquired of my patient if by any chance he came in contact with the chemical. It occurred to him that he did so in handling blueprints. In the manufacture of blueprints, treatment with a solution of chromic acid forms part of the process. A patch test with blueprint paper likewise gave a positive skin reaction, but less marked than with the acid solution.

The patient was advised to take a two months' vacation during which time the lesions healed remarkably well. He has been able to continue with his work in a comfortable manner with the use of gloves. We have, in this instance, a case of contact dermatitis in a person with an allergic background.

Dr. Coca has spoken of vegetable oils. We are hearing and reading a good deal about vegetable oils as possible allergic factors. It needs to be emphasized that vegetable oils are found only in the seed which is the last thing with which the patient comes into contact. Of course, certain aromatic oils are to be found in other parts of the plant with which we do come into contact. When we crush the leaf of a plant and perceive an odor, it is to be assumed that we are dealing with an aromatic oil. Most preparations of allegedly vegetable oils are made with the use of ether and chloroform, chiefly ether. All that we are justified in saying is that we have an ether-soluble substance. To say that we are dealing with a vegetable oil as a causative allergic factor is incorrect.

My associate, Dr. Stevens, begs me to remind you of the present day importance of food dyes which have not been mentioned. Food dyes are used extensively in confections, in cake frosting, in ice cream and butter. Less frequently yellow coloring matter is found in noodles and bread stuffs. If, therefore, we harken to the lesson of Dr. Sulzberger, our job will never be completed.

Dr. Lewis Webb Hill, Boston.—I think it would be very helpful if Dr. Sulzberger could give us a list of a few standard dyes to keep in stock to do routine testing with. I would also like to ask him if the very dark colored dyes are worse than the light blues and light pinks.

Also, if you see a young child with an eruption on its arms and legs, look out for these zipper snow suits they all wear in the winter. I have seen a good deal of trouble from them.

Dr. J. A. Rudolph, Cleveland.—An impression held by dermatologists that allergists do not see dermatitis venenata is entirely unfounded. Allergists see many such cases and obtain excellent results because of their investigative attitude. I have seen generalized dermatitis from lipstick, with skin lesion distribution which would be difficult to differentiate from dress dye dermatitis. I have also seen this same condition from hair dye. Results in contact dermatitis are very gratifying if one will take sufficient time to investigate them.

DR. FRANCIS M. RACKEMANN, Boston.—There is one interesting point about these cases that needs a little emphasis, and that concerns the time-relationships. The beginning of the lesion of the dermatitis occurs very promptly after exposure, that is, within twenty-four hours, possibly less. Of course, the patch test likewise, as Dr. Simon just said, appears in twenty-four hours. The thing that disturbs me a little is the long duration of time which is necessary for improvement after contact is broken. I would like to ask Dr. Sulzberger if he has any theories about that.

DR. SULZBERGER.—To answer Dr. Coca: I cannot make up my mind about the efficacy of the injection of fat-solvent soluble substances for treatment and for prophylaxis of contact dermatitis produced by those fat-solvent soluble excitants. I cannot make up my mind because on the one hand I seem to have clinical evidence that it works: I have treated florists that never could work with chrysanthemums; and when they received their injections of the "oil," they could work with the chrysanthemums and not get their dermatitis; I have treated patients with ragweed contact dermatitis who had their dermatitis year after year until they got the injections and then their dermatitis ceased; and I have other similar clinical evidences of the efficacy of prophylaxis with "plant oil" injections. Yet when one tries to prove experimentally that one has decreased the sensitivity of the skin of such patients, as I have done, by first patch testing these cases quantitatively, then giving them the specific "plant oil" injections and then patch testing them quantitatively afterwards, one can demonstrate no diminution of the sensitivity. The treated cases again react at approximately the same concentration at which they reacted previously. So I have become skeptical of these clinical results which cannot be backed up by an experimental method. As soon as we are able to back up the efficacy of oil injection desensitization by any experimental method, I would like to try (and I have spoken to Dr. Coca several times about that) to get the water-soluble, contact dermatitis excitants in suspension in fatty bases by emulsifying them; and then treat by injecting these water soluble excitants as emulsions in oil, as water in oil emulsions.

The question of the manner of spread which Dr. Coca brought up is very interesting, and Dr. Strauss in Dr. Walzer's institute has contributed to a very marked advance in our knowledge of how this contact-type skin sensitivity spreads. If you are not acquainted with this work, you will become so shortly because the paper has been read and it is surely in press.

In regard to the remarkable observation that so many cases of such conditions as infantile eczema, prurigo, atopic dermatitis, and many other allergic dermatoses improve rapidly in hospitals and immediately recur at home, I have for many years tried to figure out what there was in a hospital atmosphere that was different from a home atmosphere. One thought which occurred to me was that one has very little dyed clothing, very few dyed carpets and rugs, very few dyed drapes, etc., in a hospital room. The exposure to dye particles in conjugation with larger molecules of fabrics, etc., is certainly tremendously reduced in a hospital, as compared to a home atmosphere.

The two cases of urticaria which we reported demonstrate that these dyes can be absorbed and can produce the other types of sensitivity; and R. L. Mayer's work also demonstrates that very clearly. People

working with paraphenylendiamine may get not only contact dermatitis, but also asthma, vasomotor rhinitis, urticaria, and atopic dermatitis, all due to paraphenylendiamine. We must, therefore, seriously consider dyed particles in our other forms of allergy in addition to their importance in the contact type. I believe that this is perhaps the most significant part of this contribution in regard to the present audience.

Concerning the question of eosin, it seems a fact that it is impossible to make an indelible lipstick which does not contain something related to eosin. In other words, the fluorescein derivatives are those which must be incorporated in a lipstick to make it indelible and patients sensitive to that group will have to go back to using the old-fashioned nonindelible lipstick.

Regarding Dr. Duke's case of the husband being sensitive to the wife, or rather to the wife's clothes or cosmetics—cases of this type are, of course, common. We see the opposite also, that husbands are sensitive to a cosmetic that the wife does not use, to a perfume or some other ingredient. I have even seen one "man" with a lipstick sensitivity which was due to his own use of lipstick. It was very difficult to get that history from him. I eventually got it by asking him to bring in the lipstick his girl used, and he brought one in.

Answering Dr. Bernton, about the dichromate, that is, of course, a common cause of contact dermatitis.

I should like to say a word about food dyes, as possible factors in contact-type dermatitis. There are certain food dyes that may be important, but as a matter of fact I have yet to see a case which I could prove was due to the ingestion of a food dye. Orange peel, for instance, is dyed and one certainly sees contact dermatitis from orange peels. However, it is very hard to decide that it is the dye in the orange peel that does it, because orange peels contain terpenes and limonenes, which produce irritations on anyone's skin. If you take an orange peel, crush it slightly and lay it with the colored side, the outside, against the skin as a patch test, you produce eczematous and bullous reactions in almost everyone. So it is very hard to determine if it is the dye in the dyed oranges that does it. The California orange peels and also the Florida orange peels both cause these reactions. One of these types of orange peel contains no dye whatsoever.

As to Dr. Hill's question about the list of dyes, it is impossible to lay in a small stock of the usual or fundamental dyes for testing all cases. Dr. Goodman and I have 70 different dyes that manufacturers have given us, which they sell to put in lipsticks. One lipstick may contain many different dyes.

DR. HILL.—How about the mother substances?

DR. SULZBERGER.—You cannot do anything with mother substances. The specificity depends on very small alterations in these dyes, even perhaps to alterations in their physical properties. It is said that a patient may react to a dye made by one manufacturer and not to that same dye with the same formula made by another manufacturer. In these dyes there is something as yet unknown about the physical state and the way they have been prepared which confers the specificity. So it is just impossible to list these dyes. As I say, for lipsticks we now have 70 different dyes, just to test for lipstick dye sensitivity. There are literally thousands of different dyes encountered in the daily life of the average modern adult.

In regard to snow suit dermatitis, I have seen cases of that kind, just as Dr. Hill describes.

As far as concerns Dr. Rudolph's remarks, I am very glad that he sees these cases and finds the causes of them. I sometimes find the causes myself, but by no means always. I am inclined to be slightly sceptical concerning the generalized eruption due to lipstick sensitivity mentioned by Dr. Rudolph. We have seen, as I said, 14 certain cases due to lipstick sensitivity and we have probably seen as many more in which we could not absolutely prove that lipstick was the etiologic factor. I have not seen one that was generalized. I admit it may occur. However, Dr. Rudolph's description of the typical dress dermatitis localizations presented by his presumptive generalized lipstick case makes me suspect strongly that his patient was also sensitive to dress dyes. We have seen several such cases in which the patients presented, for example, cheilitis, i.e., irritation of the lips, plus contact dermatitis in localizations of dress dermatitis. These patients were then proved to be sensitive not alone to lipstick dyes but also to dress materials, particularly to red dress materials which are likely to contain some of the same dyes as the lipstick.

Answering Dr. Rackemann about the time factor; yes, that is true that it takes twenty-four hours. I have forgotten exactly what your future question was regarding the time factor.

DR. RACKEMANN.—How do you explain the long duration?

DR. SULZBERGER.—I cannot explain continuance of the eruption after elimination of exposure. It is just simply a fact and it occurs—not in all patients, but only in some. One girl patient we had put on lipstick, in spite of the fact she knew she was sensitive to it, every week end. She could not bear to go without it over the week end. She would start to clear up by Monday, and Tuesday night was all cleared up and by the end of the week she was well and ready to start over again. Our repeated observations in this case proved that she cleared up within a few days after elimination of the lipstick. On the other hand, in striking contrast to the above case, another girl put one of these dyes on her lips once and only for a few minutes and she had a flare-up which lasted for six or seven weeks following that one application, with absolutely no further contact; I cannot explain these mysterious variations; we must just add them to the multitude of mysteries for future study and elucidation.

PRESIDENT HUBER.—Dr. Sulzberger has an announcement to make.

DR. SULZBERGER.—Gentlemen, we are contemplating the formation of a new society to be called the Society for Investigative Dermatology. The object of the Society is to further the study of the skin and its reactions by investigative and objective methods.

You are all cordially invited to come to the first meeting of this society, which will be an organization meeting, and express your opinions and have the privileges of the floor. If you so desire you are invited to make application for charter membership in the new Society, all of you who are interested in furthering the investigation of the skin and its reactions. From my acquaintance with all of you and from what has been said here this morning, I am certain that many of you are intensely interested in the skin and its reactions. You are invited to come to the Hotel Dennis at nine-thirty in the morning, Thursday, June 10, 1937.

OBSERVATIONS ON THE TREATMENT OF ASTHMA AND RELATED CONDITIONS WITH SUPRARENAL CORTICAL EXTRACT (CORTIN)*†

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SINCE the isolation of the cortical hormone from the suprarenal gland, this substance has been employed empirically in the treatment of many different diseases. As knowledge concerning the functions of this hormone has been acquired by clinical and experimental investigation, an attempt has been made to apply this knowledge therapeutically, by selecting for treatment with this hormone, patients who have diseases which suggest derangement of function of the suprarenal cortex.

Inasmuch as one of the important functions of the suprarenal cortical hormone is regulation of the concentration of sodium and potassium[1-5] in the blood and the control of water balance,[6, 7] our clinical investigation on the effect of its administration to patients suffering from asthma and other allergic conditions was undertaken with the particular objective of determining whether it would lessen the excessive bronchial secretions of certain asthmatic patients, the copious nasal discharge and edema of the nasal mucous membrane of patients suffering from vasomotor rhinitis, and the swelling of the skin observed in cases of urticaria and angioneurotic edema.

LITERATURE

Few investigations on the use of suprarenal cortical hormone in the treatment of allergic conditions have been reported in the literature, and the results of these studies have been conflicting. Fineman[8] employed this type of therapy in four cases in which asthma was intractable to other forms of treatment. The suprarenal cortical hormone was administered subcutaneously and intravenously, beginning with a dose of 0.5 c.c. and gradually increasing to a maximum of 4 c.c. per dose. Injections were given three to four times weekly over a period of from two to four months. "One patient showed marked improvement, one moderate, one slight, and one no improvement." All four patients, however, gained in weight and strength, and an increase in appetite was reported.

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Cohen and Rudolph[9] gave suprarenal cortical hormone to four patients who were suffering from asthma. They used an extract of the suprarenal cortex prepared by Rogoff and called "interrenalin." This substance "was administered by mouth in amounts more than sufficient to ameliorate the symptoms in adults with Addison's disease." Treatment of one patient was continued for five weeks, and of the remaining three for six weeks. In no case did these investigators observe "the slightest change in the severity of the asthma as determined clinically or by the amount of epinephrine needed to control the symptoms."

Pottenger[10] and his associates reported favorable results in the treatment of 50 asthmatic patients. To some they gave salt (sodium chloride) and epinephrine; to some, salt and suprarenal cortical hormone, and to some salt, epinephrine and suprarenal cortical hormone. All these substances were administered by mouth. Their report is concerned with results observed within the first two weeks of treatment. Sodium chloride was administered to each patient in a dosage of from 3 to 6 gm. daily. The dosage of crystalline epinephrine employed was 1/16 grain (0.004 gm.) three times daily by mouth. The suprarenal cortical hormone used in the study was prepared by F. M. Pottenger, Jr. and was diluted so that 1 c.c. of the extract was equivalent to 10 gm. of whole, raw suprarenal gland. Of this extract, 0.5 to 1 c.c. was administered orally two to three times daily. The condition of 30 of the 50 patients was markedly improved by this treatment; that is, they were "symptom free from three months to two years." Of 18 patients, the condition was moderately improved; that is, there was "recurrence of symptoms with colds and exhaustion states." The condition of two patients was not improved. Nineteen children of this group, who were treated with resulting relief, were almost all of the type who had considerable bronchitis and bronchiectasis. In no instance did salt alone control asthmatic symptoms. The authors emphasized the importance of a program of rest for each patient in addition to the medication described in order that relief may be obtained.

Wilmer and Miller[11] treated 72 asthmatic patients, 90 per cent of whom were refractory to other methods of treatment, with suprarenal cortical hormone. This substance was injected intramuscularly in a dosage of 1 to 4 c.c. every one to seven days until a total of 20 to 80 c.c. had been administered. Complete relief was obtained by 10 individuals, or 13 per cent; partial relief by 21, or 29 per cent, and no relief by 41, or 57 per cent. Admittedly, proof that the improvement noted was due to the suprarenal cortical hormone alone is lacking but the authors stressed the fact that the patients whose condition was improved and who were relieved of their symptoms were those who

were refractory to other methods of treatment, so that, although the percentage who obtained relief was small, yet they felt that the treatment was worth while.

Pertinent to this discussion is the observation of Waldbott,[12] who expressed the belief that so-called thymic death is identical with that caused by anaphylactic shock, and he has noted that the suprarenal glands of some animals, the death of which was due to the latter condition, contained no medullary tissue. Waldbott stated that McDonald had reported eight cases of definite hypoplasia of the suprarenal glands of patients the death of whom was due to asthma. Whether this hypoplasia was chiefly of the cortical or of the medullary portion of the gland was not stated.

From the literature which has been reviewed one cannot be certain that any improvement recorded was due solely to the administration of suprarenal cortical hormone. The influence of a program of rest in bringing about amelioration of symptoms was probably an important factor in certain cases reported. It is our impression that the fate of substances, such as epinephrine and suprarenal cortical hormone, is rather uncertain when they are administered by mouth, and that the parenteral method of administration should be the one of choice in a study of this type.

METHOD OF ADMINISTRATION

Suprarenal cortical extract (cortin) prepared by Dr. E. C. Kendall at The Mayo Clinic was administered to 19 patients. Each cubic centimeter of the solution administered contained the hormone extracted from 75 gm. of whole adrenal glands of beeves. The extract was prepared for intravenous administration, contained merthiolate 1:100,000 as a preservative, and was kept in a refrigerator during intervals between administrations. Because we were dealing for the most part with patients suspected, or known, to be allergic, we were particularly cautious to carry out in each case preliminary skin tests to determine whether any sensitivity to the material existed. In no instance was hypersensitivity encountered. As an additional safeguard, subcutaneous or intramuscular injections of a few cubic centimeters of cortin were given before proceeding with its intravenous administration. After it had been determined that the patient was not hypersensitive to our extract the therapeutic dose of cortin usually employed for each patient was 10 c.c. daily on six consecutive days; it was administered intravenously. The temperature of the solution was raised to body temperature and then was slowly injected.

Each patient was instructed to increase his daily intake of salt (sodium chloride), either by increasing the amount of salt used with meals to the limit of tolerance, or by taking, orally, enteric tablets of sodium chloride. Although the amounts of sodium chloride taken

varied considerably, in each instance the amount ingested greatly surpassed the patient's normal average intake of salt. Studies of the concentration of sodium and potassium in the blood before and after treatment were not carried out.

RESULTS OF TREATMENT

Of the 19 patients who had asthma or related conditions and who were treated in the course of this study, nine who were suffering from asthma or asthmatic bronchitis did not obtain symptomatic relief and did not notice a decrease in the amount of bronchial secretion.

One patient who had asthmatic bronchitis was completely relieved of her symptoms while receiving treatment with cortin and salt. Because of the apparent excellent result in this instance, certain details of the case will be mentioned.

CASE REPORT

This patient, a woman, aged sixty-three years, complained of having had nocturnal asthma at times in the past five years, and of a productive cough of two years' duration. The sputum was profuse and foamy. The asthma was not seasonal but was worse when the patient had colds or when she was under exertion. Administration of epinephrine and ephedrine with amytal gave temporary relief. There was no family history of allergy. The patient was obese, and there was no history of loss of weight. Her weight on admission was 173 pounds (78 kg.). The systolic blood pressure was 165 and the diastolic 90 mm. of mercury; the pulse and temperature were within normal limits. A few diffuse, wheezing râles were noted. The laboratory tests, which included urinalysis, estimations of the hemoglobin, erythrocyte, and leucocyte counts, roentgenograms of the thorax, the routine serologic test for syphilis, and electrocardiographic studies disclosed nothing of significance. Intradermal tests, using a few common airborne antigens, gave negative results.

Administration of an antiasthmatic iodide mixture was started on admission and was continued during the entire period of observation.

Over a period of four days the patient received a total of 30 c.c. of cortin, 10 c.c. of which was given intramuscularly; the remainder, intravenously. Enteric salt tablets were also given with each meal. On the third day, having taken only 15 c.c. of cortin, the patient felt stronger, walked to the clinic for the first time, and had only slight asthma on rising. She was given another 10 c.c. intravenously and the following day had no asthma, felt stronger, received a final dose of cortin, and was dismissed, to continue taking salt for seven to ten days at home.

The woman had two slight attacks of asthma after she had gone home. She reduced her weight to 143 pounds (65 kg.) by January, 1936. She took iodides occasionally.

This patient returned to the clinic on October 21, 1936, stating that she had been in good health until she experienced an exacerbation of her asthmatic symptoms after having a cold in August and again in September, 1936. She felt that her previous improvement was the result of cortin therapy, and her first request on her return was for more cortin. The dyspnea and excessive bronchial secretion again disappeared in the course of a second period of treatment with cortin and salt, and she was completely relieved symptomatically. She was treated for six successive days and received 51 c.c. of cortin in all. Iodides were not used in the last course of treatment.

Six other asthmatic patients observed slight improvement while being treated, but the influence of other factors, particularly environmental change, in effecting this improvement must also be considered. This is illustrated by the case of a young farmer, sensitive to the dander of farm animals, whose asthma almost disappeared while he was being treated with cortin in Rochester, but returned immediately on his return to the farm. Other individuals, although their condition improved while under treatment, were unable to discontinue the use of epinephrine.

In attempting to evaluate any new method in the treatment of asthma, a physician always is handicapped by lack of proper controls, by the marked variations, and by fluctuations of the disease as it affects different individuals and appears under different circumstances. Clinical experience, however, would lead one to anticipate that at least half of any group of asthmatic patients will give evidence of temporary improvement while they are under observation in clinic or hospital, regardless of the type of treatment, if any, that is used. We, therefore, do not feel optimistic about the results obtained in the treatment of asthma or asthmatic bronchitis with cortin, according to the method we used in this clinical study.

Two patients suffering with vasomotor rhinitis accompanied by marked rhinorrhea did not notice change in the amount of nasal discharge or other symptoms, and the symptoms of one patient who had severe chronic urticaria and angioneurotic edema became much more distressing during the period of administration of cortin and salt; after a total of 25 c.c. of cortin had been given, treatment was discontinued at the patient's request.

REACTIONS

During intravenous administration of cortin, reactions were encountered in two cases. That the cortin, of itself, was the immediate cause of the reactions seemed unlikely, as will be seen from the following details.

The first reaction was encountered during the second intravenous administration of 1,000 c.c. of physiologic saline solution to which 10 c.c. of cortin had been added. The patient was an obese Italian housewife, aged fifty years, on whom, eleven days previously, cholecystectomy had been performed for cholelithiasis. Postoperatively, a severe, productive cough, bronchitis, and asthma complicated her convalescence. The sputum was very profuse. The first injection of saline solution and cortin was without incident but after 500 c.c. of the same mixture had been given two days later, the administration was suddenly terminated because of a severe reaction consisting of sudden collapse; cold, moist perspiration; pallor and apprehension; thready, faint pulse, and shallow and rapid respirations. These symp-

toms lasted a few minutes, after which recovery gradually took place. The cortin used was from the same supply as was that used for this same patient two days previously.

The second untoward incident occurred while the first 2 c.c. of cortin was being given intravenously to a man of forty-eight years. A preliminary intradermal test had given a negative result. The reaction consisted of a sudden feeling of faintness, pallor, and headache. The extract used was the same as that which had been used without incident in treatment of other patients. The episode clinically suggested simple syncope; it was transient, and in the next three days the patient tolerated without reaction daily intravenous injections of cortin, totalling 18.4 c.c.

SUMMARY AND CONCLUSIONS

Nineteen patients of whom 16 had asthma or asthmatic bronchitis, two, severe vasomotor rhinitis and one, severe chronic urticaria and angioneurotic edema, were given suprarenal cortical extract (cortin) intravenously. To all these patients sodium chloride was given by mouth in quantities much larger than they were accustomed to take in their diet. The intravenous administration of cortin was well tolerated for the most part, and the two "reactions" obtained were not interpreted as being due specifically to cortin.

The patient who had urticaria and angioneurotic edema apparently could not tolerate the cortin and increased amounts of salt; the two patients who had vasomotor rhinitis obtained no appreciable symptomatic relief, and likewise nine asthmatic patients seemed to receive no benefit from the use of cortin and salt by our method of administration. One patient apparently obtained relief from asthma on two occasions several months apart, while cortin and salt were being administered. Six additional asthmatic patients noted some improvement of their symptoms while under treatment, but the improvement obtained could well be accounted for in most instances by rest, change of environment, avoidance of specific allergens, or other general measures. We conclude, therefore, that intravenous administration of comparatively large doses of suprarenal cortical extract (cortin), supplemented by excessive amounts of sodium chloride given by mouth, gave little or no specific benefit to our group of patients who had asthma and certain related conditions.

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DISCUSSION

DR. ABRAHAM H. FINEMAN, New York.—In 1930 when Swingle and Pfiffner first published observations on the preparation of the cortical hormone, I tried to get some of this material with the hope of employing it in the treatment of bronchial asthma. I was impressed by the weakness, exhaustive state, hypochlorhydria, and hypoglycemia that occurs in protracted asthma, and it seemed to me that this extract might, therefore, be useful in the treatment of this condition.

In 1931, I began treatment with suprarenal cortex extract in four severe, protracted asthmatics. These patients had been studied from every angle and were treated with various forms of therapy with failure. I then employed the cortical hormone, injecting the extract subcutaneously and intramuscularly. Doses were started with 0.5 c.c. and increased up to 4.0 c.c., given three to four times weekly. At that time the extract was expensive and prohibitive for extensive study.

Our results, as the speaker just mentioned, were marked improvement in one case, moderate improvement in another, slight improvement in a third, and no improvement in the fourth. We made no glowing recommendations for this treatment at the time, but I did recommend that other men try this therapy, using larger doses, 10 c.c. at a time, first employing the subcutaneous and intramuscular routes and eventually using it intravenously. Before using the extract in our cases, intradermal tests were done with negative results and after numerous treatments were given, the patients were found to be negative on retesting. We obtained no constitutional or systemic reactions.

One striking observation about cortical hormone was that it improved the appetite, strength, and weight of the patients. We have subsequently used this preparation in children who showed loss of weight, malnutrition, and poor appetite.

We also made observations on the blood pressure and pulse rate. There were no changes as a result of this treatment. In other cases sodium chloride was given by mouth in addition to cortical hormone and no further improvement was noted.

The speaker today reported on 19 patients. This is the first report that I know of where cortical hormone was administered intravenously in bronchial asthma. One must be cautious in employing a substance of this kind intravenously for fear of a constitutional reaction.

From the results of the paper presented today, I would say that no greater improvement was obtained in this series than was obtained in ours. Dr. Milton Cohen, as you know, published a paper on cortical hormone a year or two after mine with no improvement in asthma. The Pottengers in California, however, observed some improvement, and last year there was considerable publicity over the work reported by Dr. Wilmer. I feel that his results were no better than ours.

In conclusion, I would say that cortical hormone is no panacea in the treatment of bronchial asthma. One may obtain good results in a small percentage of severe asthmatic patients. I would be very careful in administering it intravenously.

Dr. Prickman.—Concerning the tonic effect of cortin in these cases, I have recognized none. Dr. Piness mentioned the lack of uniformity in cortical adrenal extracts. Dr. Kendall's extracts are carefully standardized on adrenalectomized dogs and are used effectively in the treatment of Addison's disease. The fact that these patients tolerate large amounts of cortin intravenously demonstrates that the extracts contain no epinephrine.

MISTAKES IN ALLERGIC DIAGNOSIS AND TREATMENT

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TWO means of approach to the subject of errors in allergic diagnosis suggest themselves after our records have been reviewed. First there are those errors that are technical, of which a great deal has been said, and second there are those that are clinical. Of these there has been very little mentioned. Of course, the technical and clinical study depend upon each other for accuracy in diagnosis. We shall deal with the clinical side and show cases that illustrate clinical mistakes, which were made either by treating conditions allergically when they were not allergic, or by failure to treat them so when they should have been treated as such. The following four case histories show allergic states that were treated surgically.

CASE REPORTS

CASE 1.—F. L., female, nurse, forty-seven years of age, had a past history of migraine and two previous diagnoses of gallstones when seen with colicky epigastric pains radiating under right shoulder and accompanied by belching and vomiting. There had been temporal and basal headaches during and between attacks. Tenderness was present in right subcostal region, and the right kidney was palpable. Muscular rigidity was absent. Gastric analysis revealed diminished acidity and rapid emptying time. The blood count was normal. This was before the day of gallbladder dye studies. A surgeon operated, upon his diagnosis of gallstones, and found a normal gallbladder. Wheat was later found to react by intradermal test and its elimination from diet relieved the symptoms. Final diagnosis was wheat allergy.

CASE 2.—A married woman, thirty-eight years of age, under treatment for early spring, summer, and fall type of hay fever from 1930 to 1935. A maintenance dosage of 15,000 units of timothy and 20,000 units of ragweed had been established on a three- to four-week injection basis in 1932, but had to be reduced to 3,000 and 4,000 units, respectively, in 1932 and 1934, because of severe local and systemic reactions. Urticaria had developed. Late in the fall of 1934, there was severe epigastric colic with pains radiating under the right shoulder blade, at times accompanied by frequent urination and pains also in the right flank. The patient entered Lakeside Hospital and after failure to show the gallbadder with dye on x-ray plate a cholecystectomy was done. Chronic cholecystitis was reported found by pathologist. For six weeks pollen treatment was omitted but the gastrointestinal symptoms and urticaria continued. Pollen treatment was then resumed with a dosage of only 1,500 units each, and severe pains occurred in the right subcostal and flank regions followed by frequent urination. Tenderness was present in right flank and right lower quadrant. An x-ray showed calculi absent in urinary tract, but catheterization disclosed ureteral spasm and produced relief of pain and urination. It was repeated several times and afforded relief. On two subsequent injections of pollen, the same symptoms were produced before it was discovered to be allergic in nature. On the third attack ephedrine sulfate gave satisfactory relief. The patient was now found to be sensitive to a great many foods. These

were removed from the diet and pollen dosage reduced further to 500 units each. No further symptoms resulted except when allergic foods were added to the diet. Final diagnosis was atopy of gastrointestinal, gallbladder, and ureteral muscles with urticaria, due to foods and pollen overdosage.

CASE 3.—A radio announcer, twenty-seven years of age, married, and of a nervous temperament. He was referred to me by a surgeon on account of pains which he had been having in the epigastrium and dreams from which he would awaken stiff and sore (nocturnal epilepsy). He had a positive allergic family history. Physical examination was negative except for some tenderness without rigidity in the right lower quadrant, supposedly due to appendicitis. Three white blood counts were normal. While under study, severe pains developed in the abdomen with increase of soreness in the right lower quadrant, and a fibrous appendix with adhesions was removed. No relief of complaints followed this procedure. Allergic studies afterward showed positive intradermal reactions to pork, milk, and potato, and positive leucocytic response after consumption of milk and potato. All three articles were removed from the diet and no further abdominal colic followed. The nocturnal epilepsy was controlled by phenobarbital. Diagnosis: irritable colon due to food allergy, epilepsy, and mistaken diagnosis of chronic appendicitis.

CASE 4.—This patient who was operated upon in error was a librarian, thirty-six years of age, who came to Cleveland from the south. She had a positive family allergic history and vasomotor rhinitis for three years. Two years previous to time of examination she gradually developed pains in the epigastric region and right subcostal area with soreness to pressure, belching, and constipation alternating with looseness of bowels without blood. Studies had not shown the presence of ameba. After treatment for a year at home the appendix was removed. Removal afforded no relief. Our studies including gastrointestinal x-ray, stomach analysis, and blood were negative. The abdomen was tender throughout without the presence of rigidity or masses. Practically everything the patient ate was tested by intradermal or leucocytic reaction and a number of foods were found to react.

The diet was made up with nonreactors, omitting foods most strictly when intradermal and leucocytic reactions agreed. The patient has remained well since the diet was instituted but is ten pounds under her usual weight. Diagnosis: Gastrointestinal food allergy, operated upon in error for appendicitis.

CASE 5.—This patient presents a surgical condition, but the treatment of his gastrointestinal food sensitization renders it unnecessary to operate. The patient was thirty-eight years of age, married, male, custodian at school, and a victim of the fall type of hay fever. His intestinal symptoms consisted of pressure in epigastrium, belching, attacks of sharp pains in epigastrium, flatus, constipation, and burning in rectum. An x-ray had been taken of the gallbadder which showed several calculi. Tenderness was present in the epigastrium and right subcostal region. Stomach analysis showed increased acidity. X-ray disclosed pylorospasm, hypertonicity, and hypermotility of colon. The following positive intracutaneous reactions were obtained: wheat, milk, rye, potato, peanut, almond, walnut, pecan, and beef. These articles were omitted from the diet. The patient was seen at intervals during two years and remained sufficiently relieved of his presenting symptoms that he became a calculi carrier and refused operation.

CASE 6.—This case was one of cardiac asthma that simulated allergic asthma early in its course. The patient was a dentist, fifty-five years of age, with a negative allergic history, who had always been well until a month before seen, when he developed asthma. The paroxysms of shortness of breath came while at work and at night shortly after retiring. The nocturnal attacks would compel his leaving the bed for several hours. A cough with sticky mucus without blood was present.

Examination showed a broad chested emphysematous type of person. The percussion chest sounds were hyperresonant and auscultatory ones that were heard were much diminished with sibilant râles throughout both lungs. The heart at the time of the first examination was found to be normal as to size, rate, rhythm, and blood pressure, but the sounds were diminished and valvular. No electrocardiographic study was made at this time. Fluoroscopic and x-ray study of the chest showed increased peribronchial markings and slight dilatation of the descending aorta. Positive intradermal tests resulted from his own house dust, orris root, and feathers, but attention to elimination of these reactors afforded no relief, and the patient was not seen for a period of four months, when in consultation I saw him again in an orthopneic state, cyanosed, and sweating. The heart had dilated and left border extended to the anterior axillary line. A soft faint systolic murmur was heard at the apex and base of the heart. The heart rate was 130 per minute and force at the apex was very weak. Sibilant râles and moist râles were present in the lungs. The patient died after forty-eight hours and autopsy showed pulmonary and coronary arterial sclerosis with occlusion in left coronary artery. Fibrotic and eosinophilic infiltration was present in bronchial walls with heavy plugs of mucus in the bronchi. The mistake was made in ever considering this case an allergic one on only positive intradermal tests, but the physical signs which were present later were not at hand. However, nocturnal shortness of breath starting in a person past middle life should suggest heart disease despite allergic positive reactions.

CASE 7.—This patient was a college student who had the summer and fall type of hay fever which had not yielded to pollen treatment. The symptoms, time of year, dermal tests agreed, but it was unusual not to obtain some relief by treatment. As the boy swam daily at his summer home this was forbidden on general principles and much to our surprise no pollen treatment was needed. This case must then be included as an error for it proved to be a traumatic type of hay fever such as might follow after a nasal operation, application of drugs, etc.

CASE 8.—This patient was a married man, an office assistant, thirty years of age, with a positive family allergic history and record of fifteen years of migraine. He consulted me on account of pains beneath the right subcostal ribs which came regularly from one to two hours after meals and were relieved by soda. He had been thoroughly examined for ulcer and cholecystitis, so this work was not repeated. The blood chemistry was found to be normal and basal metabolism minus 15 per cent. Arrangements had been made at the hospital for exploratory operation in case no help was received in this last resort consultation. Fortunately, migraine developed while being studied and the pains in abdomen left but persisted in the temporal regions. He was then studied along allergic lines and found to be sensitive to wheat and rye. Elimination from the diet of these two allergens reduced the headache and pains, and use of gynergen was most satisfactory. The patient has gained in weight and is again at work. Diagnosis: migraine of cerebral and abdominal type. The patient narrowly escaped an operation on account of symptoms resembling a surgical condition.

CASE 9.—This patient was a female, aged twenty-eight years, stenographer, with a negative allergic history, whose symptoms began in May, 1936, with an intense itching in the limbs and spread over the whole body. The itching became so marked that clothing was discarded and she ran through the house violently scratching the body until long and deep excoriations were produced. The patient had been in three of our hospitals and I was the fifteenth physician to appear on the case. When seen the patient was in a pitiful state of nutrition as wheat, eggs, milk, and beef had been omitted from the diet for several months and great difficulty was being experienced in feeding of other foods. She was skin and bones and slept very little

due to itching and hallucinations of marching were disturbing. Hypnotics were used freely and it was considered to be a mental case. The weight had declined from 140 pounds to 86 and marked atrophy of all of the muscles had resulted. The skin was darkened, thickened, dry, scaly, and resembled that seen in a chronic eczema. All of the subcutaneous fat had been lost. Lesions were not confined to flexor surfaces. Scratching had made them look more like eczematous ones. No night gown was worn and when the skin would get warm the covers would be suddenly thrown off. Periodic dyspnea was present and the lungs contained sibilant râles, which were assumed to be part of the allergic reaction. Reports of x-ray findings stated that only peribronchial deposits were seen. The foods removed from the diet were the only ones to which the patient was tested and had reacted positively. One week of thorough elimination convinced me that they were not a factor. For several months it was impossible to arrive at a diagnosis but finally enlarged cervical and axillary glands appeared, and the blood showed a slight simple anemia with leucocytosis of 30,000 without abnormal cells. A gland was removed and diagnosis of Hodgkin's disease made. Mediastinal glands caused further shortness of breath and the patient developed unconscious attacks and died. This case is reported as an error because it had been thoroughly treated along allergic lines when internists should have suspected leucemia or Hodgkin's disease from the chronic infiltrated pigmented skin.

*CASE 10.—This patient was a middle-aged female who had been under treatment for cough and attacks of shortness of breath diagnosed by allergists as allergic asthma, but no relief had resulted. When seen the patient had sibilant râles only in the left chest and the pulse rate was rapid. Apical sounds were sharp and short. The unilateral chest signs of asthma brought to mind the possibility of pressure and the rapidity of heart effects of goiter. Careful examination of the neck disclosed a pulsating mass below the left clavicle. X-ray examination revealed a substernal goiter. This was removed and the asthma cured. Allergy was not a factor in this case although positive protein reactions and an allergic family history were present.

COMMENTS

It is impossible to show in the allotted time by case histories all of the cases in which errors have been encountered. The first four emphasize the importance of careful consideration of symptoms and physical signs when confronted with a surgical possibility. The presence of a surgical condition does not prove that it is the cause of the symptoms in an allergic patient, and the proving of atopy by all of the accepted means as dermal tests, history, symptoms, signs, passive transfer tests, etc., likewise does not prove it is the cause of the symptoms. In Case 2 a chronic cholecystitis was present, but it was not the cause of the symptoms in an allergic person. Cases 3 and 4 are of this nature. Operations were not curative. In Case 5 the gallstones found were not removed and the allergens excluded from diet relieved symptoms. Cardiac asthma is still confused with allergic asthma in its early onset. In middle aged patients commencing to have asthma it should be thought of first if attacks are nocturnal. Of course, later on cardiac, physical, and pulmonary edema makes the diagnosis. The mistake is made when you only see the patient once

*Drs. O. P. Kimball and Theron S. Jackson have supplied notes.

TABLE I

ILLUSTRATIONS OF MISTAKES IN DIAGNOSIS

CASE	OCCUPATION	SEX	AGE	ALLERGIC HISTORY	POSITIVE DERMAL	LEUCOCYTIC TESTS	INCORRECT DIAGNOSIS	CORRECT DIAGNOSIS	CORRECTNESS OF DIAGNOSIS PROVED BY
1	Nurse	F	47	Pos.	Yes	None made	Gallstones	G.I. Wheat allergy	Relief by diet
2	Housewife	F	38	Pos.	Yes	None made	Gallstones	Food allergy and pollen atopy	Relief by diet and reduced pollen dosage
3	Radio announcer	M	27	Neg.	Yes	None made	Appendicitis	Food allergy; epilepsy	No relief by appendectomy. Relief by diet, phenobarbital
4	Janitor	M	38	Pos.	Yes	Positive	Partial correct, gallstones	Food atopy; gallstones	Relief by diet
5	Librarian	F	36	Pos.	Yes	Many positive	Appendicitis	Food and incidental allergy	Relief by diet
6	Dentist	M	55	Neg.	Yes	None made	Allergic asthma	Coronary and pulmonary sclerosis with thrombosis	Autopsy and failure of allergic treatment
7	Student	M	21	Pos.	Yes	None made	Hay fever	Traumatic rhinitis	Removal of trauma
8	Office assis.	M	30	Pos.	Yes	Positive	Gallstones	Abdominal migraine	Diet and gynergen relieved
9	Stenographer	F	28	None	Yes	None made	Allergic dermatitis and asthma	Hodgkin's disease	Failure of allergic treatment and autopsy
10	Housewife	F	35	Yes	Yes	None made	Allergic asthma	Substernal goiter	Removal of goiter

or twice and early in the disease as shown in Case 6. Migraine with abdominal pain has misled many surgeons to needless operations. It is now intriguing the allergists. Cases 1 and 8 show where unnecessary operations were performed or contemplated. The intense early itching of Hodgkin's disease is very misleading in an atopic patient when glandular evidence has not developed as shown in Case 9. In Hodgkin's disease the skin is slightly pigmented, thickened, and no typical eczema is seen to suggest allergy. Lesions are excoriations and not confined to flexor surfaces. Glandular biopsy later, of course, makes the diagnosis simple.

In the tenth case it is doubtful if a diagnosis of asthma due to substernal goiter pressure would have been made in a patient proved to be allergic unless careful consideration of the unilateral sibilant râles and rapid heart would be given by one versed in goiter diagnosis. It recalls the necessity of making a careful physical and x-ray examination of the chest of asthmatic patients when possible.

CONCLUSIONS

1. A series of case histories has been shown illustrating errors in diagnosis and treatment.

2. Discussion of important points in the histories has been made which serves to emphasize importance of correct diagnosis.

3. The presence of positive dermal reactions and other allergic diagnostic findings in the cases shown had to be proved by clinical means to be factors of importance.

DISCUSSION

Dr. Charles H. Eyermann, St. Louis.—It is thoughtful of Dr. Lambright to share his errors with us so we can learn and thereby become better clinicians. Nothing is more helpful to one's progress than a glittering recollection of past errors, and I believe discussion of this paper will be best served if each one of us recites his errors.

The errors that Dr. Lambright has presented are those of incorrect label or incorrect organ diagnosis and concern us more as internists and diagnosticians and less as allergists and therapeutists. My analysis of these 10 cases is to the effect that 6 of the errors should be charged to the internist and 3 to the allergist. Case 5 exhibits no error, either in diagnosis or treatment, and I believe was presented to show that a patient with demonstrable organic disease can have his subjective symptoms relieved by allergic methods.

It is noteworthy to remember that six of these cases have gastrointestinal symptoms which present the greatest difficulty in differential diagnosis. Clear, unbiased judgment, accurate observation, and clinical experience with similar cases are necessary to determine in the presence of an intraabdominal mystery the necessity for surgical intervention. In the present stage of our surgical technique, it is quite natural for us to err on the side of greater safety. But a knowledge of the factor of allergy will explain many of these clinical conditions.

There are many reasons for the errors of our colleagues to be more in evidence than our own. Except in acute or fulminating conditions, our errors seldom plague us until after the lapse of time.

In addition to the errors cited by Dr. Lambright, I have seen bronchogenic carcinoma, aortic aneurism, pulmonary tuberculosis, heart disease with and without hypertension, splenomegaly, and even pernicious anemia treated as bronchial asthma. I would hasten to add, however, that the correction of our colleagues' errors is often sterile diagnostic triumphs in so far that in many cases betterment or comfort of the sick individual is not attained. My own errors which I have made in the past, which I try to avoid now, are the failure to identify chronic purulent antrum infection as a concomitant factor in vasomotor rhinitis; the failure to identify scabies as a complicating factor in allergic dermatitis or even to consider it as allergic dermatitis; the failure to seriously consider the drugs as a factor in the cause of chronic urticaria and the prolongation of chronic bronchospasm, and the failure to evaluate the rôle of overtreatment in the prolongation of vasomotor rhinitis.

Some years ago at a meeting of the Allergy Clinic Round Table which meets with the Southern Medical Association, the term allergo-internist was facetiously suggested as descriptive of the ideal allergist. From Dr. Lambright's presentation, it is evident and stressed that the good allergist perforce must be an excellent internist.

I would especially commend Dr. Lambright for his presentation for it will aid his colleagues to practice more successfully and protect humanity from misdirected zeal.

Dr. B. Kraft, Indianapolis.—I should like to report an interesting case of mistaken diagnosis. A married woman, aged thirty-two years, complained of generalized pruritus of one and one-half years' duration. Her family and personal history were positive for atopy.

Physical examination was negative except for the discovery of a slightly enlarged subclavicular gland—about the size of a pea. The blood count and basal metabolism were within normal limits. She did not improve under treatment along allergic lines based on skin tests. Results were equally unsatisfactory after trial elimination diets. Since the patient showed certain psychobiological reaction patterns she was hospitalized for rest and psychotherapy which also failed to improve her condition.

The patient had previously mentioned in conversation that a diagnosis of lymphosarcoma had been made eight months before upon her brother. As a last resort we asked for a biopsy of the subclavicular gland, expecting a negative report. To our surprise the pathologist reported lymphosarcoma.

A review of the literature on lymphosarcoma showed that intense and persistent pruritus without other symptoms is frequently an early characteristic of this disease.

Dr. Abraham H. Fineman, New York.—I have seen two children with papilloma of the larynx and I am sure many of you men have, too. One was an infant of about nine or ten months and the other a two-year-old child. Papilloma of the larynx can closely simulate asthma. Both of these children were sent into the hospital with a diagnosis of bron-

chial asthma in a moribund condition. Both had marked stridor, cyanosis, severe dyspnea, and cough. There was no fever and they looked desperately ill. Adrenalin was given with no relief.

This type of case is often erred upon and the diagnosis of bronchial asthma made, with resulting exitus. It is important to laryngoscope or bronchoscope these cases without delay and if surgical removal of the polyp or polyps seems feasible this should be done, otherwise an immediate tracheotomy is indicated. In one case where we did a tracheotomy, it was a life-saving procedure.

I mention papilloma of the larynx in this connection where mistakes in diagnosis have been made. In children of one or two years of age, with severe stridor, we must always bear in mind the possibility of such a condition.

DR. FRANCIS M. RACKEMANN, Boston.—Some years ago I took care of a very nice elderly lady who had hay fever. She arrived in a nice limousine with a chauffeur, and she was a very nice person. I thought that the quicker I could get her in and get her out, the better for both of us, and so I did not make any physical examination routinely.

Some time after that another doctor called up and said that he believed I had seen Mrs. X last year, and I said, "Yes, sir."

He said, "How much sugar did she have at that time?"

DR. WARREN T. VAUGHAN, Richmond.—A lot of the apparent errors are justified. I mean we have them coming to us. A lot of them are due to lack of cooperation on the part of the patient. Just one example in which I felt sure I was right but I could not prove it. This was several years ago when intermittent hydrarthrosis was first considered to be possibly an allergic condition. I had a patient with a very typical intermittent hydrarthrosis. She was 4-plus allergic to wheat, a perfectly clear-cut case, and I advised wheat avoidance. She did not want to avoid wheat. She was a young girl and had been accustomed to having her own way. So I told her that there was no way in which she could get over her intermittent hydrarthrosis. She continued to eat wheat and about three months later she had her appendix out. She has not had an attack of intermittent hydrarthrosis in the succeeding ten years!

DR. M. I. LOWANCE, Atlanta.—One thing that has not been mentioned that we see so much of in the extreme south is syphilis in the negro. It is so often overlooked in asthma, and when the syphilis is cured or treated properly, the asthma ceases. The same applies to spirochaetosis of the lung which we see quite frequently down there and which is very commonly confused with ordinary asthma.

DR. GEORGE L. WALDBOTT, Detroit.—As to Dr. Eyermann's remarks, I believe the reason for confusing early asthma with other pulmonary conditions is the fact that its clinical picture simulates that of bronchial pneumonia or "influenza" resulting from an infected allergic edema of the lungs.

DR. HARRY L. HUBER, Chicago.—A few years ago a gastroenterologist asked me to give pollen treatments to one of his patients. During the course of treatment she was sent to the hospital by him as she had

complained to him of periodic recurrences of her gastrointestinal symptoms. He made x-ray and laboratory studies and no pathology was found to explain these symptoms. I was not consulted until after this study had been made as I was supposed to be an allergist and not an internist. My pollen treatments were resumed and we found that the gastrointestinal symptoms appeared within two hours after each treatment and persisted for as long as forty-eight hours. At the close of the season perennial treatments, at three-week intervals, were attempted but were stopped as each injection precipitated abdominal symptoms. The next season treatments were started but were discontinued again for the same reason. This case illustrates the necessity of close observation of all patients under treatment.

DR. LAMBRIGHT.—I want to thank the discussants for their remarks and I think all Dr. Peshkin said was correct. However, I only reported 10 cases and you cannot draw very definite conclusions from that number. We all make mistakes but I do not think any more mistakes are made in allergy than in any other specialty.

ALLERGENIC MOLDS IN THE PACIFIC NORTHWEST*

PHILIPP SCHONWALD, M.D.
SEATTLE, WASH.

THE relatively high humidity† and the considerable incidence of rainy weather in the coastal regions of the Pacific Northwest cause an abundance of molds. A study of the atmosphere revealed the following, the spores of which are air-borne:

Alternaria nigrescens
Alternaria tenuis
Aspergillus niger
Aspergillus oryzae
Hormodendrum cladosporoides
Penicillium digitatum
Penicillium expansum
Penicillium italicum
Rhizopus nigricans
Trichoderma koningi

The most abundant mold is *Rhizopus.* Innumerable colonies of this common mold appear on our mold plates throughout the rainy season. *Penicillium expansum,* the mold which causes the decay of apples, is next in frequency and continuous occurrence. *Trichoderma koningi,* a very common soil fungus, is a close third. All the others, while appearing on mold plates throughout the year, occur far less in numbers (Charts I and II).

A total of 145 mold plates were exposed, and the colonies identified and counted. Exposures were made in the heart of the city of Seattle, in residential districts, and at different points along the coast. There is apparently not a great difference in the species of fungus spores all along the Pacific Coast.

A continuance of these observations through several years will show whether there is a seasonal regularity to the occurrence of mold spores in the air. It seems, however, that the study of the general environment, that is, the atmosphere at large, may be of secondary importance so far as mold spores are concerned. We have found it necessary and of considerable advantage to explore the individual environment of our patients; namely, the atmosphere in their houses or workshops, in order to determine which molds are most abundant in the environment where the patient lives and works.

A total of 150 allergic patients were tested for mold allergy. Only individuals whose history suggested a possible mold allergy were subjected to those tests which, in most instances, were performed by the

*Read before the Thirteenth Annual Meeting of the Association for the Study of Allergy, Atlantic City, June 8, 1937.

†Even during the summer months the average humidity in the morning in Seattle is around 85 per cent, declining toward evening to about 51 per cent. The corresponding figures for Spokane, which is about 300 miles inland, are 42 and 27 per cent.

PHILIPP SCHONWALD, M. D., F. A. C. P.

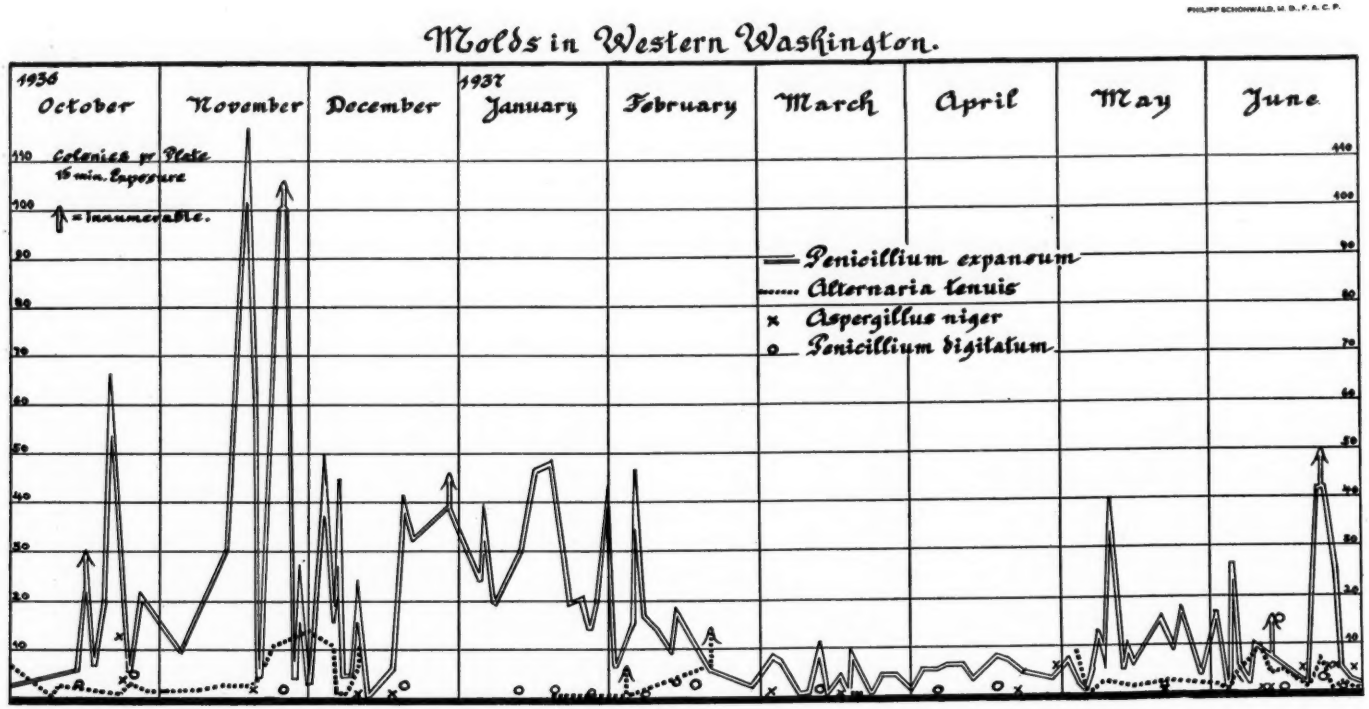

Chart I.

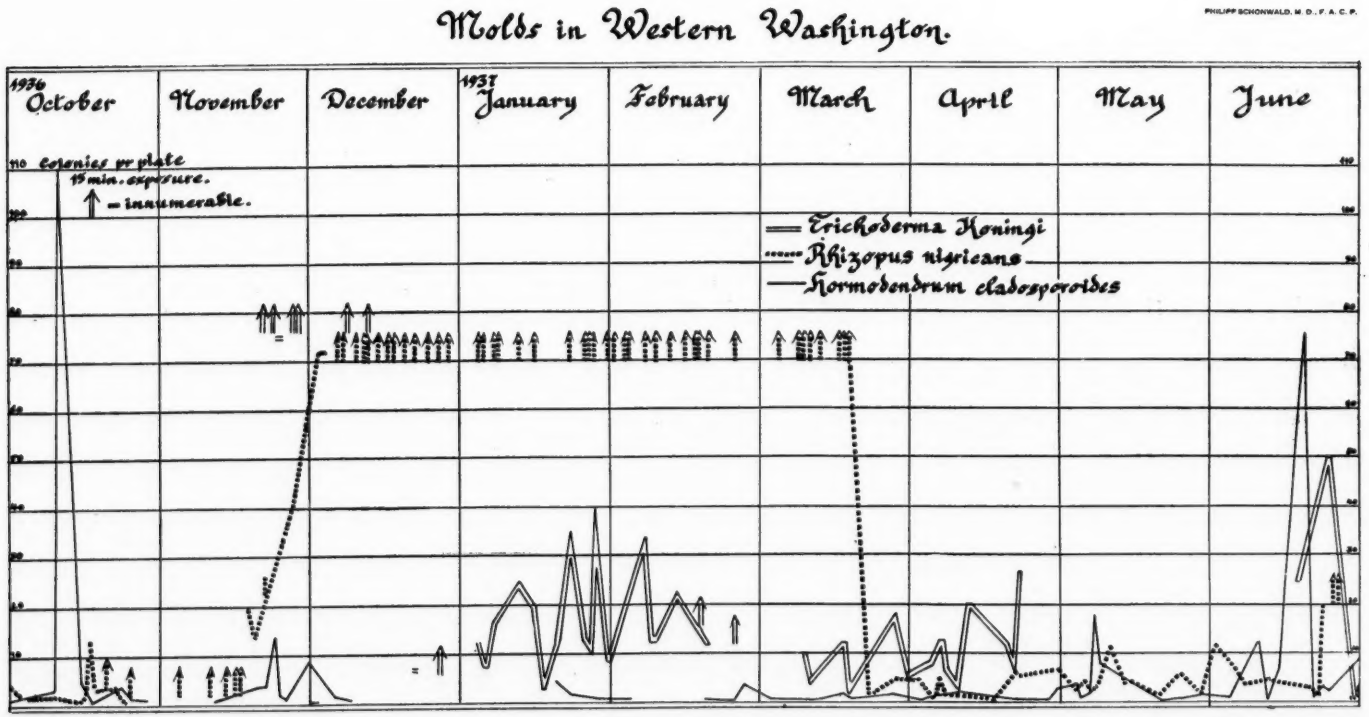
Molds in Western Washington.
PHILIPP SCHONWALD, M. D., F. A. C. P.
1936
October
November
December
1937
January
February
March
April
May
June
110 colonies pr plate
15 min. exposure.
↑ = innumerable.
= Trichoderma Koningi
..... Rhizopus nigricans
— Hormodendrum cladosporoides

Chart II.

scratch and by the intradermal method. In most cases sensitization to several molds was encountered. Chart III shows that *Rhizopus* is apparently the least allergenic of the molds, while the *Penicillia* and *Trichoderma* lead in the percentage of positive reactions obtained.

Of the 150 cases tested (Chart IV), all of which gave a history suggesting sensitization to fungi, only 5 did not react to any of the mold extracts. Thirty were not treated, and 29 had insufficient treatment at the time of this report. Of the 86 cases sufficiently treated, 66 or 76.7 per cent, showed definite improvement, obviously due to treatment with mold extract or to the addition of mold extract injections to other anti-allergic treatment.

Nine of the 66 improved cases were found sensitive only to molds (Chart V), although they were tested for other allergens. All of these

Chart III.

Clinically Important Molds In Western Washington.

	Total Cases Tested	Scratch Test		Intradermal		Total Positive
		+%	−%	+%	−%	
Alternaria tenuis	73	69.2	30.8	71.4	28.6	70.%
Aspergillus niger	105	59.3	40.7	80.3	19.5	68.6%
Penicillium digitatum	57	57.1	42.9	88.9	11.1	67.5%
Penicillium expansum	108	66.1	33.9	91.8	8.2	77.8%
Rhizopus nigricans	39	33.4	66.6	66.7	33.3	41.%
Trichoderma koeningi	75	64.7	35.3	87.5	12.5	72.%

patients obtained complete relief in a comparatively short time. These were four patients with asthma, two with perennial rhinitis, one who presented both conditions, one patient with dermatitis of the face, and one patient with eczema.

Fifty-seven of the improved cases had a diversified sensitization. In 22 their mold allergy was complicated by pollinosis, in 9 cases by food allergy, and in 26 instances by both pollen and food sensitization. Twenty-four of the 57 patients had hay fever, 17 asthma, and 10 asthma and hay fever. The remaining 6 showed different allergic symptoms (Chart VI). Most of the patients had been under treatment for their pollen or food sensitization, and the addition of proper treatment with mold extract undoubtedly improved the results of previous management.

Mold extracts are prepared similar to pollen antigen, from the dry pellicle. A malt medium is used, containing 10 per cent agar, which

produces a rich, spore-bearing fungus growth at room temperature. Testing is done preferably with a dilution of 1:100,000 (by weight). Treatment usually begins with the same dilution, is given subcutaneously, and the dosage advanced as in pollen extract treatment. Improvement usually follows after a few injections if the proper mold extract is used. It is advisable to carry treatment through to at least a 1:1,000 dilution, and to repeat the optimal dose once weekly for several weeks. Local reactions are rare, but sometimes delayed reactions occur. General reactions were not seen.

Chart IV.

Resumé Of 150 Cases Tested For Mold-Allergy

Total Tested	Not Treated	Insufficient Treatment	Negative Reactors	Total Treated	Unimproved	Improved	Positive Result
150	30	29	5	86	20	66	76.7%

Chart V.

9 Cases Reacted To Molds Only	
4	Asthma
1	Asthma And Per. Rhinitis
2	Per. Rhinitis
1	Dermatitis herpetiformis
1	Eczema
9	Complete Relief

Chart VI.

57	Cases Improved
22	Reacting To Molds & Pollens
9	Reacting to Molds And Foods
26	Reacting to Molds, Pollens & Foods
24	Hay-Fever
17	Asthma
10	Asthma + Hay-Fever
1	Laryngitis
1	Asthma + Eczema
2	Eczema
1	Psoriasis
1	Migraine & Asthma

SUMMARY

A study of the air-borne mold spores in the atmosphere of the Pacific slope is presented. The frequency of positive reactions to mold extracts is demonstrated. Results of 86 cases treated are shown.

Mold spores are important atmospheric allergens in the Pacific Northwest. They are sometimes the only cause of allergic symptoms, but more often a pertinent contributing factor. Proper mold extract treatment is of definite value in these cases.

718 Fourth and Pike Bldg.

GOLD CURVE OBTAINED WITH ALLERGIC BLOOD SERUM

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A CONSIDERATION of allergic phenomena with the accompanying edema and discharge of serum and mucus leads one to the belief that the mechanism involved is one of chemical changes. Disturbances in the water balance, or in the combination of water with the protein molecule or group of molecules would seem to be at fault. Instead of the presence of an abnormal substance, there may well be an absence of some factor which maintains complete solution of the body proteins in the water of the living cell. A combination of both factors is probably responsible for allergic lesions.

The allergic reaction is manifested most commonly by swelling. This edema is caused by excess fluid both in the cells and between the cells. That protein is present is shown by the fact that allergic edema fluid will dry with the formation of a crust. Cells that are swollen, when examined under the microscope, show granular changes in the protoplasm, indicating a loss of solubility of the protein fraction in the water of the tissues. This loss of solubility is not necessarily due to the lack of fluid or to its concentration, but is probably caused by the loss of some intermediate substance which combines the water with protein molecules or amino-acids or combination of both in the cells. The concentration of this substance is not uniform throughout the body as is shown by the fact that allergic reactions vary in intensity in different areas.

The protection of colloidal mixtures against electrolytes by the presence of protein solutions is commonly known. The addition of blood serum to a colloidal gold solution will protect it from precipitation by relatively strong solutions of sodium chloride. However, if the serum is diluted sufficiently and progressively there is reached a point where it loses its ability to protect the colloidal solution from precipitation against the action of electrolytes.

To determine whether blood serum from allergic individuals differed from normal serum, the following experiments were carried out.

EXPERIMENTAL

In the first experiment, five tubes of 1 c.c. of 10 per cent NaCl were set up. In the first tube 0.1 c.c. of colloidal gold solution was placed, 0.2 c.c. in the second tube, and so on for five tubes. In all the tubes there was a change of color from red to blue.

The second set up was with 1 c.c. of the gold solution in five tubes, then in order from 0.1 c.c. to 0.5 c.c. of 10 per cent NaCl solution was added. The color changed from red to blue in all the tubes.

However, when taking the same set up but using smaller amounts of the NaCl solution, a gradient of color change was obtained. By using a 1 per cent NaCl solution and starting with 0.15 c.c. and increasing the amount slowly in each successive tube, the color change was a gradual one from the original red to the blue obtained by the complete precipitation of the gold solution.

The next experiment was with 1 c.c. of the gold solution in five tubes. Next was added in order 0.05 c.c., 0.1 c.c., 0.15 c.c., 0.20 c.c., and 0.25 c.c. of blood serum. This was followed by the addition of increasing amounts of salt solution. It was found that once the system of gold solution and blood serum had become stabilized, the addition of 1 c.c. of 10 per cent salt solution could not cause its precipitation, or change in color. This same experiment was repeated but only 0.05 c.c. of blood serum was added to the tubes of gold solution. Again the presence of strong solution of electrolyte did not produce color change or precipitation.

In the next set up, six tubes of 1 c.c. of gold solution were used. A normal blood serum was diluted 500,000 times, and 0.02 c.c. was added to each tube. Next 0.02 c.c., 0.05 c.c., 0.1 c.c., 0.15 c.c., 0.2 c.c., and 0.25 c.c. of 1 per cent salt solution were added to the tubes in order. Within a short period, a progressive color change was noted starting in tube 3 and increasing to tube 5; tubes 5 and 6 showing complete precipitation. This same set up was done with the exception that serum from an allergic patient was used. The color change made its appearance in the first tube and was complete in the fourth tube. This shows a very definite and apparent loss of protection to the gold solution by the allergic serum which did not occur when normal serum was used. As will later be shown, this loss of protection shows a definite decrease of some component of the blood serum in the allergic individual as compared to the nonallergic. This same set up was made with more gradual steps in the dilutions. The changes were more gradual but present nevertheless.

The next serum experimented with was from a patient with an atopic dermatitis. This patient had had a generalized eruption but at the time the blood was taken the condition had improved. This case showed a shift in the colloidal gold curve coloring of one tube, but not as much as in a patient with severe asthma.

Serum was obtained from a case of lichen planus. The above experimental procedures were carried out with the result that the curve obtained was the same as with normal serum.

At this point a peculiar circumstance occurred. Normal blood serum was diluted 1:100,000 with normal salt solution and had stood for an hour because it could not be used at the time. When it was used it gave no protection, precipitation of the gold solution occurring in all the tubes, as if there had been no serum present. At first this

was explained on the basis of hydrolysis destroying the serum molecule. Also, the possibility that in such dilute solutions of serum, the serum molecules, if allowed to orient themselves in the serum-salt solution mixture, may have established an equilibrium, was considered. In that case, most of the serum molecules would be found adhering to the surface of the container or combined with the salt and thus be removed from the field of action, none being left free to attach themselves to the gold particles and protect it from precipitation by the salt.

Experiments were then made to ascertain the effect of aging the serum on the curve obtained. The experiment disclosed the following facts: Old normal serum gave less protection and old allergic serum gave greater protection than fresh allergic serum. In the case of the normal serum it may be due to the agglutination or precipitation of some component of the serum, while in the allergic serum, hydrolysis may have taken place, giving more serum molecules to protect the gold solution. The real reason is not known, but aging of serum does interfere with many other tests where it is used in diagnostic procedures.

Distilled water was substituted for normal salt solution as the diluting fluid for the serum. The result was a more gradual change than when the salt solution was used. The same was done by using a 3 per cent dextrose solution in distilled water. This gave a curve comparable to that obtained with distilled water.

Realizing the fact that if the serum was allowed to stand after diluting it, and that there was a change in its properties occurring rather rapidly, it was thought best to devise some other method of making the dilution. One c.c. of gold solution was placed in each of six tubes. One-tenth c.c. of whole serum was then placed in tube No. 1, and the mixture agitated by drawing the liquid in and out of the pipette, blowing some air through it each time. One-tenth c.c. of this mixture was then transferred to tube No. 2, and the same procedure gone through and so on with each tube.

With normal blood serum in this method of procedure, the color remains unchanged in the first and second tubes, and from there on to the last there is a gradual change in color from the original ruby to violet to blue black. With serum from allergic patients, a curve is obtained in which the color change begins one tube ahead of the normal control. Also the color changes are greater, with more of a trend to the blue.

It seems that once the curve has been established, the addition of an excessively large amount of electrolyte does not change it.

It was found that after diluting serum with distilled water 1:100, 0.1 c.c. of the mixture added to gold solution caused a definite change in color. When 0.1 c.c. of 1:10,000 dilution of serum was added to 1 c.c. of gold solution there was a still greater change. This may be due to the serum molecules clumping and absorbing the gold particles

on its surface in the first case. In the second case it may be due to the relatively few serum molecules neutralizing the electrical charge on the gold particles and thus permitting them to agglutinate and precipitate.

Normal blood serum was diluted 1:500,000. One-tenth c.c. was added to 1 c.c. of gold solution. No color change resulted. By adding 0.12 c.c., 0.13 c.c., 0.14 c.c., and 0.2 c.c. to successive tubes, a gradual color change was obtained. When doing the same with allergic serum, the color change was more marked. In this case the nuclei of agglutination were probably fewer in the latter instance, thus producing fewer and larger particles with the consequent darker color.

Experiments were made with positive luetic serum, not allergic. This showed no change over that of the normal control. The serum procedure was tried with positive and normal spinal fluid. Again there was no difference between luetic and normal serums.

There is a great difference in the sensitivity of various lots of colloidal gold solution. One lot required the further addition of salt solution before the color curve could be obtained.

Mienicke antigen was tried and the resultant gradation in sedimentation was greater with allergic serum than with the normal control. This was repeated with luetic serum. The Mienicke reaction was 4-plus. It was found that lues apparently has nothing to do with the curve obtained.

Cataphoretic measurements of the particles in the tubes show that with the change in color there is an accompanying decrease in the electrical charge, which is less where there is complete precipitation of the particles than where there is no color change or precipitation. This indicates that precipitation of the gold solution occurs when the electrical charge on the particles is neutralized.

SUMMARY

1. Colloidal gold curves obtained with serum from allergic patients differ from those when normal serum is used.

2. The character of the curves leads one to infer that allergic blood serum is lacking in some protein that is present in normal serum.

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Special Reports

CONTAMINATION OF SYRINGES USED FOR SKIN TESTS*

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THE great increase in recent years in the use of the skin test as a diagnostic procedure constitutes sufficient reason for a careful investigation of the technical factors involved in the various types of skin tests. An excellent general discussion of this subject is given by Walzer.[1]

Skin tests are frequently done by the intradermal method, which involves the use of a syringe and needle. The possibility of error resulting from chemical contamination of the syringe by substances previously used in testing (or treating) with the same syringe has been called to our attention by several authors.[2-8] It is practically impossible to cleanse a syringe thoroughly by washing with water and there are many substances, such as tuberculin, ragweed, and other pollen extracts, etc., which are not destroyed by boiling. Hence sterilization by boiling, which destroys bacteria, does not prevent chemical contamination with heat-resistant substances previously contained in the same syringe. Thus, one may obtain a false positive Schick test in a tuberculin-sensitive patient because the syringe used for the Schick test previously contained tuberculin, which was incompletely removed in the cleansing process. A test to egg in a ragweed-sensitive patient may be falsely positive because the syringe used for the test previously contained ragweed pollen extract.

This possibility of syringe contamination may be forcibly demonstrated by the following simple experiment:

A 1 c.c. all-glass syringe of the "tuberculin" type, made of clear, colorless (or slightly colored) glass, is filled with a solution of a dye, such as a saturated aqueous solution of gentian violet or methylene blue. The syringe is emptied by forcing the plunger down to the zero point. It is then washed five times in water, not by drawing in water through the needle end of the syringe, but rather by removing the plunger and allowing water to run in the opposite end. Water is also allowed to run over the plunger, which is reinserted and forced down to the zero point with each washing. Inspection of the syringe after

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five washings reveals a very definite staining of its inner, ground-glass surface. This presence of dye in the syringe is still quite marked after 50 washings. This dye, however, does not remain permanently adherent to the syringe; it gradually "wears off" and is expelled in small quantities as the syringe is used. These facts may be demonstrated as follows:

A small quantity of water (0.05 c.c.) is drawn into the syringe. The plunger is moved back and forth several times and a drop of the fluid expelled through the needle onto a white porcelain surface. This drop of water is found to be definitely colored even after the syringe and needle have been washed 50 times, as described above. A color comparison may be made between this drop of water and similar drops containing known concentration of dyes. This comparison was made in two cases and it was found that the concentration of dye expelled from the syringe, after 50 washings with water, varied between one part of the original solution in one thousand to one part in ten thousand. (The standard dye solutions were made, of course, with syringes not previously used for dyes, a separate syringe being employed for each dilution.) This concentration is well within the range of activity of such common allergens as ragweed pollen, egg, tuberculin, etc. (Hay fever patients frequently give positive skin reactions to pollen extracts containing one part of pollen to one million of extract.)

The conclusion to be drawn from this experiment is evident; namely, that syringe contamination by substances previously used in the same syringe may constitute a serious source of error, resulting in false positive skin reactions.

Two objections may be made to this conclusion: first, that we are not justified in comparing dyes with allergens; that dyes may be more adherent to ground glass than the substances used in doing skin tests. This objection is not sustained, as shown by the following evidence:

An intradermal test was made with physiologic solution of sodium chloride, in a ragweed-sensitive patient, with a previously unused syringe and needle. The test was negative. The same syringe and needle were then filled with a 1:50 dilution of ragweed pollen extract, the contents expelled and the syringe washed 50 times with water, as described above. Physiologic solution of sodium chloride, 0.10 c.c., was then drawn into the syringe from the same flask as the control test, the plunger moved back and forth several times, and an intradermal test made on the same patient. It was definitely positive. The syringe was then boiled in water for ten minutes and another test made with physiologic solution of sodium chloride. It also was definitely positive.

The second objection is that we often use very dilute extracts in doing intradermal tests; that it is not fair to compare a 1:100,000 dilution of ragweed pollen or egg white with a concentrated solution

of a dye. To a certain extent this objection is sustained for the following reason: if it is possible to reduce the concentration of dye solution expelled from a syringe from undiluted to 1:1,000 dilution by washing the syringe in water, we might expect to reduce the concentration of an allergen from 1:100,000 to 1:100,000,000 by washing. This dilution is probably beyond the range of apparent activity of the allergen in skin testing, and hence (if this is true) it would not give a false positive skin test.

On the other hand, however, when skin tests are negative with dilute extracts, we frequently find it desirable to use more concentrated extracts. We often use strong extracts for desensitization. Some physicians still use the glass syringe with asbestos wound plunger, which, no doubt, presents greater opportunity for absorption. If, therefore, we wish to have thoroughly reliable skin tests it certainly is desirable to use a given syringe for only one test substance, and, furthermore, never to use that syringe for a weaker concentration of the same test substance.

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POLLEN DERMATITIS

Report of a Case

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POLLEN dermatitis has been discussed widely in medical literature. Hannah[1] in 1918 was first to point out its existence. Brown, Milford, and Coca[2] not only recognized the condition but traced its etiology to the fatty fractions of pollen. It was then Sulzberger and Wise[3] who, following the studies of earlier workers on dermatitis *venenata*, emphasized the value of patch or contact tests in the diagnosis of this problem. The excellent reports on the treatment of ragweed dermatitis by Brunsting and Anderson[4] and Brunsting and Williams[5] show that the present methods of treatment of pollen dermatitis are only partially successful.

I should like to report an unusually severe case of pollen dermatitis due to timothy and ragweed pollens, the method of treatment employed, and the results of treatment:

CASE REPORT

J. N., aged thirty-three years, was referred to me for diagnosis and treatment in February, 1935, at which time he was symptom free. His history was briefly that, on July 4, 1926, he became afflicted with an itchy eruption which was confined largely to the hands, forearms, neck, and face. At first the rash appeared as small vesicles which in the patient's own words "were so itchy that he scratched until the blisters broke." These vesicles increased in number and size until the entire exposed surface of the body was covered. His face, and especially the eyelids would become so edematous, and his general discomfort so great that it was necessary to hospitalize him for at least three months. This attack would gradually subside and by the first of the year he would be completely well. The above reaction and course recurred regularly each year at approximately the same time, until the summer of 1935.

The atopic family history in this patient is marked, involving his own daughter, a sister, a niece, and a nephew. This history of course could explain his late summer coryza each year but would not account for his contact dermatitis. It was necessary, however, to test him both by patch and cutaneous tests to find that he gave a positive patch test to timothy pollen oil and to dwarf and giant ragweed pollen oil. He gave a moderate reaction to the aqueous extract of dwarf and giant ragweed intradermally. A large variety of patch tests were completely negative. Tests to the ordinary foods, inhalants, and bacteria were done intradermally, and he reacted only slightly to several of the foods which were not taken into account at that time. General examination, serology and other laboratory tests were negative.

The question of treatment was then considered. In the light of the severity of his problem and the lack of sufficient evidence that alcoholic or ether extractions of pollen gave more than just slight to fair relief,

and also in view of our own lack of satisfactory results in other cases of pollen dermatitis by the usual treatment, the following course of treatments was considered logical. Inasmuch as this man was a city dweller and rarely frequented the country, it was decided that an extract containing the whole pollen grain would have all of the sensitizing ingredients and so would possess similarly, all hyposensitizing constituents. A 20 per cent emulsion of timothy pollen in almond oil was prepared by suspending 20 gm. of dry pollen in 80 c.c. of oil. A similar suspension was made of combined dwarf and giant ragweed pollen. Dilutions from the pollen emulsions were made in sterile almond oil to 1:600, 1:100, and 1:10. Increasing doses of this emulsion were then given in the gluteal area at weekly intervals beginning with 0.01 c.c. of the 1:600 dilution in February and increasing progressively to 0.5 c.c. of the 1:10 dilution. Mindful of the concomitant aqueous pollen therapy for his hay fever, the treatment was given cautiously. This treatment was given continuously through the entire summer and has been continued to the present.

RESULTS OF TREATMENT

During the entire summer of 1935, his hay fever was completely controlled. His skin with the exception of three or four very small vesicles in his mustache area was completely free of itching and vesiculation. The same result was obtained in 1936, with this notable exception, that upon riding out into the country with the windshield of his automobile open and wearing a sport shirt, he suffered some slight irritation of his neck and face which cleared completely in three days.

CONCLUSION

It is believed that the great improvement in the dermatitis over previous years was due to injections of pollen suspended in oil.

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654-656 HANNA BUILDING

Annual Review

ALLERGY AS RELATED TO OTOLARYNGOLOGY AND OPHTHALMOLOGY

LITERATURE FOR 1937

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A REVIEW of the literature on the subject of allergy from the standpoint of ophthalmology and otolaryngology for the year of 1937 shows a comparatively small number of presentations devoted to this subject. In general, there appears to be a growing interest in the part played by allergy in paranasal sinus disease. On the whole, however, the more radical methods of surgical treatment predominate the more conservative nonoperative or minor operative methods. In the compilation of statistical results in the treatment of sinus disease, the allergic and the nonallergic conditions are considered as a single group. The classification of these cases into the allergic, the infectious, and the allergic with infection should be considered in discussing these cases from the standpoint of diagnosis and treatment.

Arslan[1] was able to produce the Arthus' phenomenon in the velum pendulum palati of rabbits by means of a submucous vela injection of horse serum repeated at regular intervals. The development of the Arthus' phenomenon was found to be slower in the oropharyngeal than in the submucous tissues of rabbits, and the oropharyngeal lesion is smaller than the subcutaneous lesion, probably because the reactivity of the submucous tissue to local sensitization is diminished as compared to that of the subcutaneous tissue. The same experiments carried on in guinea pigs failed to produce the Arthus' phenomenon in the oral mucosa.

Studies on the supposed relation between autonomic imbalance and the color of the septum were undertaken by Bilchick.[2] Investigations of this type are particularly interesting in view of the changes in the color of the nasal mucosa observed in nasal allergy. Bilchick confirmed Bernheimer's[3] observations by showing the absence of relation between the color of the septum and autonomic imbalance. In a series of 100 cases, no relation was found between the color of the septum and blood pressure, blood sugar, blood nitrogen, basal metabolic rate, or red cell count (except in severe anemia).

Clarke and Rogers[4] report a statistical study of 162 cases of allergic or vasomotor rhinitis. It is noteworthy that 73 per cent of the patients

had already had one and 20 per cent had two or more operations on the nose and throat. Fifty-one per cent showed positive skin reactions to one or more inhalants although in only 10 per cent were the reactions markedly positive. All tests were done by the intracutaneous method. This series of patients did not include patients reacting to pollen. House dust was found to be the most frequent cause of reactions producing positive reactions in 75 or 46 per cent of the entire series. Next in frequency were feathers and orris root. There were only seven reactions to food.

Vollmer[5] has made an investigation of the use of the benzedrine inhaler in acute colds, sinusitis, and allergy in children. The idea of the investigation was to determine the feasibility of administering benzedrine to children by dry inhalation, the therapeutic effect of such inhalation, and the possible occurrence of toxic effects. It was used in 75 cases of acute rhinopharyngitis and sinusitis with relief of the obstructive symptoms. In asthma, the nasal obstructive symptoms were definitely relieved. No untoward effects were noted from the use of the inhaler.

Fenton and Larsell[6] carried out a series of experimental and clinical studies on several substances resembling ephedrine. In a considerable series of private patients, the effects of these substances on the inferior turbinate were tested by swabbing on a 1 per cent solution, and in a smaller series the solution was dropped into the nose with the head reversed with the following results: Tetrandrine methiodide in a 1 per cent and in 0.5 per cent solution produced a pinkish precipitate at room temperature after twenty-four hours; hence, it was used only a few times. Shrinkage was rather marked, but complaints were made of its bitter taste and tendency to produce slight burning. Hordenine methiodide in a 1 per cent solution produced fair shrinkage, slight sneezing and burning, and a rather persistent bitter acid taste. Benzyldimethylamine methiodide in a 1 per cent solution gave an excellent shrinkage with little or no burning but was slightly bitter. Betaphenylethylamine in a 1 per cent solution produced fair shrinkage with slight burning and a fairly bitter taste. No evidence of systemic absorption or of changes in pulse or blood pressure was noted.

The value of these substances would seem to lie in their clinical use in relatively acute conditions, after determination of necessary pharmacologic factors, particularly for benzyldimethylamine methiodide and betaphenylethylamine.

According to the investigations of Fitzhugh,[7] neosynephrin is chemically related to epinephrine and ephedrine. He found neosynephrin hydrochloride superior to epinephrine hydrochloride and ephedrine hydrochloride as a cardiovascular stimulant. It is as good, but not superior, to, epinephrine hydrochloride in increasing the efficiency of infiltration anesthesia. It is less toxic than epinephrine hydrochloride

or ephedrine hydrochloride. It produces constriction of longer duration than that produced by ephedrine hydrochloride and there are no apparent undesired effects.

In addition to ionization, the use of escharotics locally has also been employed by recent observers in the treatment of nasal allergy. Lewy[8] recommends the local use of resorcinol. He states that the proportion of successes has been considerably greater than with any other treatment and the reaction less. Resorcinol is applied in the form of a watery paste over the entire nasal mucosa including the middle meatus, after a preliminary application of 3 per cent cocaine. He found that relief from this treatment may last for a few weeks to several months and in a number of cases treated about two years ago there has so far been no recurrences. Its use in the treatment of ragweed hay fever has not been encouraging.

Wenner and Alexander[9] reported some very interesting observations on the effect of zinc ionization and galvanic current on the reactions of the nasal mucosa to vasomotor drugs. Their experimental studies showed that changes in the nasal mucosa following zinc ionization do not hinder the absorption of vasomotor drugs instilled into the nasal cavity. The blood vessels and the cavernous tissues of the nasal mucosa fail to react to vasoconstrictors and vasodilator substances for six weeks after zinc ionization and four weeks after treatment with the galvanic current. It is believed that this failure of the vascular structures to constrict or dilate is due to a temporary paralysis of the vasomotor nerves or to a loss of vascular tone. Histologic studies of the blood vessels, however, showed no thickening or other pathologic change in the wall of these structures that might account for this temporary disturbance of the vasomotor mechanism.

A recent report by Alden[10] on ionization of the nasal mucosa in allergy summarizes his observations to date. He states that certainly desensitization is still the method of choice in the treatment of nasal allergy with ionization being reserved for those cases where the obstructive and secondary symptoms are predominant and where the mechanical relief to be expected is more than commensurate with the tissue damage incident to ionization. He found that asthma was not lessened after ionization except in a few cases. He finally concludes by stating that ionization produces in the nasal mucosa mechanical changes which render it less susceptible to vascular and secretory reactions. He does not believe that ionization alters either the allergic status of the individual or the ability of the nasal cells to be affected by allergens. Finally, he points out that the value of ionization rests solely upon its efficiency as an agent to reduce excessive nasal intumescence, and hypersecretion.

Fox and Harned[11] noted that the nasal mucosa of hogs offers a resistant tissue for experimental purposes because the incidence of rhinitis

in this animal is low. They have tried various methods of obtaining extracts of the nasal mucosa. The protein elements seem to cause severe reactions. An attempt is being made to obtain a material of a hormone nature. They used a protein-free extract which appeared to give some promising results when used both orally and hypodermically as a protection against colds. While no definite conclusions are as yet drawn from the results obtained, the use of these extracts, in some cases, has been striking. The possibility of a nonspecific effect, however, cannot be eliminated, especially in those instances in which the rhinitis may be of an allergic nature.

Mithoefer[12] stresses hypothyroidism of a low grade as a cause of chronic sinusitis. He found hypothyroid state associated with intestinal stasis and signs of a pale nasal mucosa. The question always arises in these cases as to whether one is actually dealing with a state of hypothyroidism or nasal allergy. Diagnosis of nasal allergy should be based on the history of the symptoms and the finding of eosinophiles in the nasal secretions. It is generally known that the hypothyroid state may or may not be associated with nasal allergy.

The matter of diagnosis and treatment of conditions simulating sinus disease was discussed by Slack.[13] He brings out the point that patients often complain of nasal symptoms, such as increased discharge, nasal obstruction, and headache which may be caused by some general systemic disorder or certain local conditions entirely unrelated to the paranasal sinuses. He further emphasizes that before instituting any therapeutic measure or advising operative procedues, it is absolutely essential that the patient be given a thorough medical examination and diagnostic study. Among various conditions which may commonly simulate sinus disease, Slack enumerates the following: neurasthenia, allergic conditions, infected teeth, refractive errors and eye strain, syphilis, intracranial conditions, disturbances of the endocrine glands, improper diet, undulant fever, and encephalitis. In the diagnosis of allergic conditions in the nose, especially the atypical types, it is very important to determine absolutely whether or not an allergic condition exists, and it is well to bear in mind, therefore, that nasal disturbances may be present which simulate allergy but are caused by some local or general systemic condition which is in no way related to allergy.

Mittermaier[14] has suggested the use of a new contrast medium for x-ray examination of the sinuses which is especially useful in those cases in which there are polypoid changes in the mucous membrane. The contrast medium used consists of barium sulfate to which tragacanth has been added. This medium is found most suitable because of its tendency to adhere to the mucous membrane. It was found to outline the contour of the mucous membrane and yet leave the cavity of the sinus free so that an air space remains.

In discussing the matter of indications for radical sinus surgery, McLaurin[15] expresses the following opinion regarding chronic hyperplastic sinusitis with polypoid formation. He believes that the presence of these conditions is a definite indication for radical surgery. At the same time, he believes that allergic therapy should be carried out. Regardless of the type of surgery employed, he does not expect much permanent benefit unless general measures directed toward relieving an essential allergic tendency are carried out. Attention is called to the former belief that hyperplastic changes in the sinuses were primarily of infectious origin. He emphasizes now, however, that these conditions should be considered primarily of allergic origin with few exceptions. In some cases of hyperplastic ethmoiditis with polyps, only the removal of polyps with proper control of the allergic state is advised. The presence of secondary infection, however, McLaurin believes, is an indication for radical types of sinus surgery.

Haiman[16] attributes failure of surgical treatment in diseases of the sinuses to an underlying allergy. He reviews the possible etiologic factors, also calling attention to the possible part played by endocrine gland disturbances. He feels that these patients should be treated primarily on an allergic basis and that operations on the sinuses should not be performed unless frank suppuration of the sinuses is present.

Harbert[17] calls attention to the diversity of opinion among various observers on the subject of sinusitis and asthma. He believes that the differences reported are due to an absence of control series of cases, accuracy in diagnosis, standardization of cures, observation over an insufficient period of time, and finally, failure to consider the allergic process as the primary factor. He calls attention, also, to the high incidence of positive roentgenographic evidence of sinus disease in these cases. He properly emphasizes that these changes are not an indication for operation but merely represent varying degrees of sinus edema. He favors the conservative methods of treatment, paying particular attention to the allergic state and later considers whatever surgical procedures are necessary.

A study of the frequency of nasal lesions in asthma and the value of operations on the nose in such cases was reported by Jacquelin and Chait.[18] Four hundred and thirty patients were studied. In 48 cases the nose was found to be obstructed and in 26 infectious manifestations, such as rhinitis and sinusitis were noted. Various operative procedures, such as irrigations of the sinuses, resection of the septum, etc. were undertaken. On the whole, while the condition of a small number of patients improved, many showed no amelioration and several even became worse. It was concluded that asthma in itself is no indication for nasal operation.

Fox and Harned[19] report their observations on the treatment of asthmatic patients in otolaryngologic practice. Various surgical and

nonsurgical procedures were carried out. One hundred and fifty private and clinic patients were included in each group. Among those treated surgically, only radical procedures were performed. Forty patients received the benefit of complete exenteration of all sinuses. Forty had intranasal radical ethmoidectomy and Caldwell-Luc operation on both sides. Fifty had only intranasal radical ethmoidectomy and 20 with suppuration had one or both antrums operated on by the Caldwell-Luc technique. In summarizing the results from surgical treatment, it was stated that among the patients whose sinuses were totally exenterated, 60 per cent were cured; when only bilateral ethmoidectomy and exenteration of the antrums was done, 45 per cent were clinically cured; when ethmoidectomy alone was done, 32 per cent were cured, and when one or both antrums was exenterated in suppurative cases, 60 per cent obtained five-year relief. In addition to these, 34 patients whose age or other conditions made them poor operative risks, received the benefit of only removal of polyps or other minor surgical treatment plus irradiation. In only three of these patients, or 9 per cent, was a five-year cure obtained. In the nonsurgical group of 150 patients, 16 adults with pronounced changes in the chest were given injections of iodized poppy-seed oil without other treatment. None remained free from asthma longer than six weeks after treatment was terminated. It is noteworthy that subsequent roentgenograms revealed the presence of roentgenopaque material as long as two years after this treatment. In a second group of 24 patients, treatment consisted of instillation of autogenous antivirus into the chest. Four, or 16 per cent, were entirely free of asthma for nine months or more, the longest period being thirteen months. Twelve, or 50 per cent, were free from asthma for six months, and the rest had freedom from asthma for from two to five months. A third group of ten persons was given injections with material taken from asthmatic patients during operation. Because of the development of abscesses following the injection of this material, it was discontinued. Another group of ten patients was given injections of serum taken postoperatively of persons with sinusitis and asthma. Of these patients, only three were free from asthma from six to ten weeks. Seventy-five patients were given injections of pseudoglobulin. The results with this material, on the whole, were reported as good.

In a study of 455 consecutive allergic patients, Bernton[20] encountered 71 who claimed that a cold was responsible for their asthmatic seizures. Twenty-seven of the patients were ten years old or under. In this connection the value of the cytologic study of the nasal and bronchial secretions should be emphasized in making an accurate diagnosis in these cases, otherwise it is not infrequently difficult to differentiate between an allergic exacerbation and an acute infection.

Woodward[21] emphasizes that there has been almost universal disregard of the staphylococcus as a potential pathogen in the nose, pharynx, and

bronchi in spite of the high percentage of staphylococcus reported in numerous bacteriologic studies made of these regions. In the treatment of acute sinusitis, chonic sinusitis, and chronic sinusitis with chronic bronchitis and bronchiectasis, Woodward has found the use of staphylococcus toxoid and staphylococcus antitoxin to be of definite value. This type of treatment should be of particular value in the management of infections complicating allergic conditions in the nose, sinuses, and bronchi.

The value of bronchoscopy in asthma and related clinical conditions was emphasized by Clerf.[22] He believes that bronchoscopy should be given a trial in the treatment of cases of bronchial asthma that do not respond to the usual methods. He found that the best results were obtained in patients with tracheobronchitis, excessive secretions, or bronchial obstruction. He found vaccines obtained from the bronchoscopically removed secretions to be of value in bacterial asthma.

Stokes[23] calls attention to the symptoms of asthma as being an indication of a possible tracheal or bronchial obstruction secondary to and associated with the pulmonary lesion and stresses the importance of bronchoscopy in cases of tuberculosis that present symptoms of asthma. He reports the case of a woman, aged thirty-nine years, in whom a diagnosis of chronic tuberculous tracheobronchitis was made. There was a mural stenosis caused by a granulomatous hyperplasia of the mucosa. Stokes believes that cases of known pulmonary tuberculosis complicated by signs and symptoms of bronchial asthma should have the benefit of a diagnostic bronchoscopy before resorting to allergic investigation.

Various forms of pulmonary atelectasis in children are described by de Bruin and Gerlings.[24] Attention is called to the physical and radiological signs by which this affection can be diagnosed with more or less certainty. The desirability of early diagnosis is indicated by the fact that within a very short time irremediable changes can take place in the occluded lung field, by which the development of bronchiectasis is promoted. Therefore, the application of bronchoscopic aspiration in cases of lung collapse is indicated as soon as possible. A number of case reports are given in detail emphasizing various points in diagnosis and treatment by bronchoscopy. It was shown that the occlusion of the bronchus by mucus plugs may produce the same effect as a foreign body in the production of atelectasis. No doubt in many cases of bronchiectasis in children, especially those with asthma, the condition may originate as a result of plugging of the bronchi with mucus which is followed by secondary infection.

In discussing the subject of tuberculous tracheobronchitis, Samson[25] and his coworkers call attention to the varied symptomatology of this condition. Among the various signs and symptoms, it is noteworthy that persistent inspiratory or expiratory wheezing is not infrequently present. Attacks of asthmatoid breathing with prolongation of one or

both respiratory phases, they state, are frequently mistaken for asthmatic bronchitis. Bronchoscopy is not considered contraindicated in active pulmonary tuberculosis. Bronchoscopically, the following types of tracheobronchial lesions are recognized, although any patient may show a combination of lesions: (1) Nonulcerative and nonstenotic, characterized by circumscribed infiltration and thickening and often by submucosal tuberculoma formation; (2) hyperplastic, characterized by submucosal proliferation and tuberculoma formation; and (3) ulcerative, diffuse or circumscribed loss of mucosa.

Menzel[26] reported that in 33 per cent of 23 patients with vasomotor rhinitis, an examination of the blood by Lowenstein's culture method gave positive results. In these patients the nasal symptoms were the only complaint, at least there were no subjective or objective signs of tuberculosis. A subfebrile temperature was rarely present and in some instances there appeared to be evidence of former pulmonary disease as shown by thorough examination of the lungs. On the basis of these observations, Menzel believes that in a considerable percentage of cases of so-called vasomotor rhinitis, a tuberculous infection is a possible cause of the allergy. It is difficult to determine from this report whether the cases of so-called vasomotor rhinitis were true allergies. According to the experiences of allergists in general, the occurrence of tuberculosis associated with nasal allergy is certainly not a common coincidence.

In a group of 1112 patients with hay fever and asthma studied by Waldbott[27] and his associates, tonsillectomy was performed in 228 before the onset of allergic symptoms and in 205 after allergic manifestations had developed. In the latter group, definite relief occurred in 1.9 per cent, temporary relief in 1.9 per cent, and aggravation of allergic symptoms occurred in 11.6 per cent. In a control group of 60 patients subjected to tonsillectomy after they had been under observation, the results were about the same. When tonsillectomy was performed for conditions other than allergy, it was successful in 35.2 per cent of the allergic group and in 36.4 per cent of the preallergic group as compared with 72 per cent improvement recorded in normal controls (Kaiser). Among 228 patients subjected to tonsillectomy before the onset of allergic symptoms, 14.4 per cent developed allergic manifestations within three months, 29.3 per cent within six months, and 48.6 per cent within two years after the operation. This compares with 26 per cent showing frankly allergic symptoms within three months; 47 per cent within six months, and 63 per cent within two years. The patients whose tonsils were removed for the relief of nasal colds and bronchitis, tonsillectomy was of more benefit in the earlier age groups. The operation was less successful when performed during the pollen season. Although the results of tonsillectomies were disappointing, the authors believe that tonsillectomy should be performed in patients having frequent infections. In others with allergic catarrh of the upper part of the respira-

tory tract which may or may not involve the tonsils, they believe that tonsillar tissue is a definite asset to the system and should be preserved.

Woods[28] gives an excellent summary of the present status of the relationship between allergy, iritis, and conjunctivitis. He describes three types of allergic conjunctivitis, first, the acute edematous type, characterized by sudden onset, edema, conjunctival congestion, and lacrimation. This type is most commonly seen with asthma and hay fever. The second type is the so-called edematous eczematous type, characterized by eczema of the lids and neighboring skin, edema of the lids, profuse lacrimation, conjunctival congestion, and slight chemosis. This type is that caused by drugs such as butyn, atropine, etc. This type is always accompanied by marked hypersensitiveness of the skin as shown by positive patch tests with the offending substances. The third type is the chronic recurrent irritative conjunctivitis often associated with low grade folliculosis with sharp exacerbations and normal bacteriologic findings. Pollens, epidermals, foods, etc., may be the cause, and the conjunctivitis may be the only manifestation of allergy in the individual. Woods discusses at some length the relation of staphylococcus toxoid to conjunctivitis. He reviews our present understanding of the nature of vernal catarrh and enumerates the reasons for classifying it as an allergic disease.

Woods further states that certain types of recurrent uveitis and iritis are allergic reactions resulting from sensitization and intoxication of the tissues by bacterial products. He believes that there is little justification for the use of vaccine therapy in the treatment of recurrent iritis because of the difficulty in determining the causative organism.

Cutino[29] discussed various allergic eye diseases, such as the conjunctivitis associated with hay fever, vernal conjunctivitis, and a few other diseases which may also be contributed to allergy; namely, phlyctenular conjunctivitis, parenchymatous keratitis, sympathetic ophthalmia, endophthalmitis anaphylactica, episcleritis, iritis, ulceration of the cornea, and marginal blepharitis. The importance of food sensitization as well as contactants and inhalants is emphasized.

Plumer[30] reports a case of retinal allergy. The patient was a physician, aged thirty-five years, who complained of blurring of vision of the left eye, of sudden onset, and of two weeks' duration. There was a reduction of visual acuity, blurring of vision of the left eye, and a slight congestion and haziness of the left macula. Removal of the tonsils and infected teeth resulted in the condition clearing up. A few weeks later, however, there was a recurrence of symptoms. At the onset the patient had ingested peanuts. There was a personal history of migraine, hay fever, and intolerance to chicken meat. Positive skin tests were obtained to chicken meat, early grass pollens, beans, cottonseed, and peanuts. Removal of these substances from the diet resulted in the clearing up of the symptoms.

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Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL FEINBERG, M.D., CHICAGO

Successful Treatment of Persistent Extreme Dyspnea "Status Asthmaticus." Herrmann, G., and Aynesworth, M. B.: J. Lab. & Clin. Med. **23**: 135, 1937.

Theophylline ethylene diamine was used in 16 cases of severe asthma in which the usual palliative treatment had become unsuccessful. These cases were all instances of asthmatic bronchitis or chronic bronchial asthma presenting attacks of "status asthmaticus." The injections were given intravenously in doses of 0.24 to 0.48 gm. diluted to 10 c.c. with normal saline. Of the 41 injections given, 31 gave prompt, complete, and persistent relief. In two instances the treatment failed to produce good results. Adrenalin sensitiveness was restored in practically all asthmatics who had become adrenalin-fast.

Reactions to the drug were common and consisted mainly of a feeling of warmth, nausea, and vomiting. Rarely were the reactions markedly disturbing.

The Action of Theophylline with Ethylene Diamine; On Intrathecal and Venous Pressures in Cardiac Failure and on Bronchial Obstruction in Cardiac Failure and in Bronchial Asthma. Greene, J. A., Paul, W. D., and Feller, A. E.: J. A. M. A. **109**: 1712, 1937.

Previously these authors and others had demonstrated the effectiveness of theophylline with ethylene diamine on the dyspnea of cardiac failure. In the present series of experiments, they were attempting to explain the mechanism of this effect. They studied normal subjects, patients with cardiac failure, bronchial obstruction due to bronchial asthma with chronic pulmonary disease, and patients with allergic asthma. Intravenous administration of 0.48 gm. of theophylline with ethylene diamine diluted to 30 c.c. with physiologic sodium chloride solution given over a period of three to five minutes caused a fall in venous and intrathecal pressures. The authors interpret this to mean that the dyspneic symptoms in these conditions are correlated with a rise in these pressures and that the beneficial effects of this drug are due to a lowering of these pressures. In 11 cases of asthma, good symptomatic results were obtained. Many of these had been adrenalin-fast.

I. The Psychogenic Factor in Asthma. II. Asthma in Adults. Strauss, E. B.: Guy's Hosp. Rep. **87**: 273, 1937.

Thirty unselected cases of asthma in adults were examined with a view to determining the presence of "nervous," psychic or emotional factors in the asthma syndrome. The "nervous" element was found to be strongly present in 16 cases, definite in 9 cases, feeble in 4, and absent in 1 case. Psychic participation takes various forms:

(1) Complex, determined; (2) an allergic person who is temperamentally a deviant from the conventional normal of his immediate social group is likely to develop asthma; (3) an asthmatic individual may make his asthma the center of his life. The asthma attack may act as an arbitrary reflex reinforcement; (4) allergic

subjects who live under extreme emotional strain are liable to exhibit the asthma syndrome; (5) asthma in an allergic subject may be part of an anxiety state, the height of which may be an asthmatic attack as an expression of an autonomic reflex outlet.

The author suggests that psychotherapy should reinforce specific and physical forms of treatment. The form of psychotherapy is to be determined by the history of the patient. It may be analytical, personality analysis, modification of environmental conditions of patient, and suggestion.

The Incidence of Major and Minor Allergy in the Deep South. Pipes, D.: South. M. J. **30**: 1012, 1937.

In a community (Jackson, La.) of 700, comprising secondary school children and college students, an inquiry was made as to the occurrence of allergic symptoms. Of these, 95 or 13.6 per cent had major allergy while 217 of the remainder (35.8 per cent) had minor allergic manifestations. In the major group, hay fever occurred 59 times, asthma 39, migraine 25, urticaria 30, eczema 10, angioneurotic edema 1, and colitis 1. Among the minor group, indigestion was mentioned 108 times, urticaria 46, eczema 46, migraine 14, hay fever 15, asthma 3, colitis 3, and angioneurotic edema 1 time. Foods at the top of the list as a cause of minor allergy were cabbage, onion, melon, strawberry, tomato, banana, chocolate, pork, peach, beef, peanut, cucumber, radish, crab, and oyster.

Food Allergens. A Statistical Study of Forty-Three Cases Relative to the Genetic Classification of Foods. Withers, O. R.: South. M. J. **30**: 918, 1937.

Withers studied 43 patients with respiratory allergy who had clinically proved vegetable food sensitiveness. In general, he found that there is not as close an agreement between foods and antigens as there is in their botanical relationship. A patient who is sensitive to one food in a botanical family has about a 50 per cent chance of being sensitive to others in the same family. If he is sensitive to the least common etiologic factor of the family, he is more likely to be sensitive to other members of the group. It is interesting to note that practically no clinical relationship was found to exist between potato and tomato of the Solanaceae family. Tomato, wheat, peanut, watermelon, peach, apple, orange, onion, and English walnut were the most common etiologic factors in their respective families.

Kapok and Molds: An Important Combination. Wagner, H. C., and Rackemann, F. M.: Ann. Int. Med. **11**: 505, 1937.

Since it is common observation that old kapok as employed in mattresses, pillows, and furniture develops a substance capable of producing skin reactions and respiratory allergy in some individuals, the authors planned a series of experiments aimed to demonstrate the method of production of this substance. They subjected new kapok, extracts of which gave negative or almost negative skin reactions, to a number of procedures and tested the extracts of the treated material on the same individuals by skin tests. Kapok fiber which had been sterilized did not develop the skin-test principle as a result of aging (six months), while exposed to light, dark, or cold. Repeated exposures to oxygen or carbon dioxide had no effect. They found that molds will develop the active principle in both kapok and cotton, especially if the molds are taken from samples of old kapok, old cotton linters, or house dust. In most of these individuals, the mold extracts alone do not give reactions. The authors conclude that the active skin-test principle in old kapok depends on the interaction of the kapok and the molds growing in it.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., NEW YORK CITY, AND JOSEPH GOODMAN, M.D., BOSTON

Experimental Arsphenamine Dermatitis: The Influence of Vitamin C in the Production of Arsphenamine Sensitiveness. Cormia, F. E.: Canad. M. A. J. **36**: 392, 1937.

The author demonstrated that in guinea pigs given a diet low in vitamin C the injection of 0.15 mg. of neoarsphenamine resulted in a more intense reaction to the initial injection than was previously encountered in a series of normal guinea pigs. Investigation of a group of nine guinea pigs previously sensitized to neoarsphenamine and then found not to be hypersensitive during a subsequent summer revealed that four developed immediate flare reactions to neoarsphenamine when tested after they had been placed on a diet low in vitamin C. A group of 14 guinea pigs in which the author had previously been unable to produce hypersensitivity to neoarsphenamine was placed on a diet deficient in vitamin C. Tested after two weeks of this diet, three of the animals showed immediate reactions (within twenty-four hours) which indicated existing sensitization, and four showed delayed reactions indicating the development of sensitization. All of this group died before a second test could be done. Twenty-two animals were given large doses of vitamin C (50 mg. daily) for twenty-eight days. None of these animals reacted to an injection of neoarsphenamine at the beginning of the experiment or to a repeat injection at the end of the twenty-eight days. However, after a further twenty-eight days of the same diet without vitamin C, seven of the twenty-two animals developed immediate reactions to neoarsphenamine.

On the basis of these findings, the author recommends intensive vitamin C therapy for patients with arsphenamine dermatitis.

Experimental Arsphenamine Dermatitis: Observations on Its Allergic Nature with Special Reference to the Schultz-Dale Phenomenon. Arch. Dermat. & Syph. **36**: 970, 1937.

The author injected guinea pigs with neoarsphenamine as in the experiments described in the previous abstract. The sensitivity of these animals was investigated by the Schultz-Dale technique (controlled by adequate observations on nonsensitized animals) using baths which included Ringer's solution plus neoarsphenamine (1:10,000 dilution), Ringer's solution with neoarsphenamine and serum from guinea pigs sensitized to neoarsphenamine, and Ringer's solution with neoarsphenamine and serum from normal guinea pigs. In eleven actively and two passively sensitized animals there was no definite evidence of positive Schultz-Dale reactions. Uteri from four of the eleven actively sensitized animals showed only minor contractions which were not greater than the contractions of the same uteri after the addition of normal serum.

The Significance of Skin Tests. Miescher, G.: Zentralbl. f. Haut- u. Geschlechtskr. **57**: 481, 1937.

The test must be adequate to the pathologic process which it is supposed to detect. Some processes of hypersensitivity have mainly an epidermal character (= eczema), while others work through an exclusively intracutaneous mechanism (urticaria, drug, and serum eruptions). These forms necessitate two varieties of skin testing, epicutaneous and intracutaneous. When doing epicutaneous tests, one

has to differentiate between the phenomena of toxic and allergic reactions. Experience has shown that there is no way of distinguishing morphologically between toxic and allergic reactions; this is possible only if one takes into consideration the quantitative factor of these tests. The toxic reaction can, as a rule, be elicited in patients who react negatively by increasing the concentration of the substance tested, while an allergic reaction can be elicited only in hypersensitive individuals and an increase in concentration in such cases merely leads to a toxic reaction.

Intracutaneous tests for hypersensitivity are partially based upon an acute vascular irritation, for example, the urticarial wheal (immediate reaction); they are based partially upon inflammatory processes, as for example, the tuberculin type reaction (late reaction). Immediate reactions are important in urticarial dermatosis, late reactions in questions of sensitivity in infectious diseases. Intracutaneous tests depend on a variety of influences, such as the changing resorption capacity of the skin and the quantitative and qualitative reactivity of the vegetative nervous system. Skin tests are extremely important in the investigation of dermatoses due to hypersensitivity, in particular as proof in occupational dermatoses. In the future, these tests will probably play an important rôle when giving advice to young people in regard to their occupational future, not so much to detect existing hypersensitivities as to test the resistance of the skin against certain substances which are known to be potential causes of skin changes leading to later sensitization. The causes of several important, allergic dermatoses, e.g. (circumscribed), neurodermatitis; chronic eczemas, and eczemas of bacterial origin cannot as yet be elucidated through skin tests. This fact does not speak against the value of skin tests, but it shows that one is dealing with a very complicated reaction mechanism.

Immunology

UNDER THE DIRECTION OF MATHEW WALZER, M.D., BROOKLYN

Effect of Heparin on Anaphylactic Shock in the Guinea Pig. Doxiades, L., and Lemke, H.: Klin. Wchnschr. **16**: 1061, 1937.

The authors studied the effect of heparin administration on anaphylactic shock in guinea pigs. The animals were sensitized to horse serum and shocked twenty-one days later. The amount of heparin needed to render the blood of guinea pigs uncoagulable was determined. This dose was injected into the sensitized guinea pigs one to twenty minutes before the shocking dose was administered. It was found that with the injection of heparin five times the usual shocking dose of antigen was needed to produce anaphylactic death. This indicated to the authors that the uncoagulated state of the blood increased the resistance of the animal to anaphylactic shock.

Histamine Studies. Riesser, O.: Arch. f. exper. Path. u. Pharmacol. **187**: 1, 1937.

The author describes a modification of the recently proposed technique of Barsoum and Gaddum for the determination of histamine in the blood and tissues. Further studies on histamine in human beings are reported.

The bloods of asthmatic and tuberculous patients showed no higher histamine content than did those of normals. Histamine was shown to be present in the sputums of both asthmatic and nonasthmatic patients. It was increased in those cases in which pus was present in the sputum.

Stimulation of the cervical vagus in narcotized guinea pigs did not result in an increase in the lung histamine content. Rabbit skin "in a state of allergic inflammation" (Arthus) contained from four to ten times as much histamine as did normal rabbit skin.

Heightened and More Lasting Tuberculin Allergy Produced in Guinea Pigs by Treatment with Killed Tubercle Bacilli in Combination with Lanolin and Vaseline. Hensel, G.: Beitr. z. Klin. d. Tuberk., 1937.

Previous workers demonstrated the production of tuberculin allergy in guinea pigs by the injection of dead tubercle bacilli into the skin and into various organs. In this communication, the author reports that the tuberculin allergy thus produced can be intensified and its duration lengthened if the killed tubercle bacilli are given in lanolin or vaseline. This results in a more prolonged period of absorption. The writer found that as little as 1 mg. of killed tubercle bacilli in lanolin was sufficient to produce tuberculin hypersensitiveness in guinea pigs.

Comparative Results of the von Pirquet Test and the Tuberculin Patch Test. Hiro, Y., and Takahashi, S.: Monatschr. f. Kinderh. **70**: 381, 1937.

In this paper the writers give an excellent review of the available literature on the tuberculin patch test and describe the results which they obtained with comparative tests on 1,000 children under ten years of age, using both the von Pirquet and tuberculin patch techniques. They performed the tuberculin patch test by cleansing the forearm with alcohol-benzine and applying one drop of old tuberculin which they covered with a square of adhesive. A drop of saline under adhesive was used as a control. Both the patch test and the von Pirquet test were graded according to the intensity of the reaction.

Of the 1,000 cases studied, 296 or 29.6 per cent gave a positive Pirquet and 232 or 23.2 per cent a positive patch test. Both tests agreed in 76.4 per cent of cases. Six hundred and eighty-one cases were negative to both tests. Although these figures indicated that the tuberculin patch test was slightly less sensitive than the Pirquet test, the authors were of the opinion that the patch test could be used for diagnostic purposes. They noted that the greatest variation in the results obtained with the two techniques occurred in the mildly sensitive cases.

On the Inflammatory Reaction, After Tissue Damage by Cold, in Sensitized and Nontreated Rabbits. Contribution to the Study of Pathergy. Billman, F.: Virchows Arch. f. path. Anat. **300**: 378, 1937.

The author compared the inflammatory reactions in sensitized and normal rabbits resulting from the application of intense cold.

Rabbits were sensitized by five intraperitoneal injections of hog serum at four-day intervals. Eight days after the last injection carbon dioxide spray was applied to the right thigh and ear of these animals and to the same areas on normal rabbits. Shortly before this procedure, the animals had been given 5 c.c. of hog serum intraperitoneally in order to induce a protracted shock. Histologic tissue studies were then made at various intervals.

At six and at twenty hours after the shock dose, the treated areas of the sensitized animals manifested only mild protective reactions on histologic examination. The inflammatory reaction became pronounced in the sensitized rabbits only after forty-eight hours. The normal animals showed these changes much sooner. The inflammation in the sensitized animals was characterized by greater vascular damage than occurred in normal animals treated in a similar manner.

The author believes that the delay in the response of sensitive rabbits was due to the protracted shock which had been induced in them. The diminished respiratory quotient which Abderhalden reported as occurring during anaphylactic shock was offered as a possible explanation of these phenomena.

A Study of the Heteroallergic Reactivity of Tuberculin-Desensitized Guinea Pigs. Higginbotham, M. W.: Am. J. Hyg. **26**: 197, 1937.

The author reports her studies on reactions of tuberculous guinea pigs to intracutaneous injections of bacteria other than the tubercle bacillus. The term heteroallergic reaction indicates an altered reactive capacity of tuberculous animals to other bacteria.

The author observed that tuberculous allergic guinea pigs reacted with a greater cellular exudation than did normals to intracutaneous inoculation with *Bacillus coli, Staphylococcus aureus,* and *Brucella suis.* The daily subcutaneous injection of tuberculin in the allergic animals to the point of abolition of the reaction to tubercle bacillus, resulted in a decrease but not in a complete loss of the heteroallergic reactivity of these animals. Tuberculous allergic guinea pigs, desensitized with tuberculin, still manifested positive complement fixation reactions.

Studies on the Sensitization of Animals with Simple Chemical Compounds. Landsteiner, K., and Chase, M. D.: J. Exper. Med. **66**: 337, 1937.

In previous communications, one of the authors reported on sensitization in guinea pigs following the intracutaneous or superficial administration of a number of simple chemical compounds. Animals thus treated exhibited increased reactions to subsequent intradermal injections of these compounds and responded with erythematous reactions when a solution of the excitant was spread on the skin. It was also reported that artificially conjugated proteins (azoproteins) could sensitize anaphylactically to the conjugate, the reactions being specific for the substance linked to protein.

In the present paper, the authors investigated the simultaneous production of skin sensitiveness and anaphylaxis by the repeated intracutaneous injections of picryl chloride and 2:4 dinitrochlor-benzene. Guinea pigs were sensitized by 15 daily intracutaneous injections of 0.0025 mg. picryl chloride in 0.1 c.c. saline. A heightened response to the injection usually began to be manifested from six to eight days after the first dose. Following a period of two or three weeks after the last injection, one drop of a 2 per cent solution of picryl chloride in olive oil applied to the belly usually resulted in a positive test, indicating the presence of skin sensitization. It was also possible to induce typical anaphylactic shock when picryl protein conjugates were given intravenously. The presence of antibodies in the serum of the guinea pigs sensitized by intradermal injections of picryl chloride was demonstrable by passive transfer by means of the Schultz-Dale technique. Precipitins to picryl protein were detected in some of the serums. Attempts to transfer skin sensitiveness passively by means of these serums have been unsuccessful.

Animals sensitive to picryl chloride could be desensitized by the subcutaneous administration of picryl-guinea pig serum prior to the intravenous shocking dose. No noticeable influence on the degree of skin sensitiveness resulted from this procedure.

The writers are of the opinion that the cutaneous manifestations are probably due to antibodies, perhaps of a special sort, produced and fixed in the skin. The authors believe that "it would be most unlikely that the two specific sensitization effects induced at the same time by intradermal injections of 'nonantigens'; namely, skin sensitivity and general anaphylaxis, are without a fundamental relationship."

Otolaryngology

UNDER THE DIRECTION OF FRENCH HANSEL, M.D., ST. LOUIS

Chronic Sinusitis: A Complete Operation, Technic and Results in 200 Consecutive Cases. McKenzie, W. R.: South. M. J. **30**: 1077, 1937.

In an analysis of 200 consecutive cases of chronic sinusitis, McKenzie discusses the matters of complete operation, technique, and results obtained. The statement is made that in chronic sinusitis where there is a true hyperplasia or polypoid degeneration of the nasal or sinus mucous membrane, any method of treatment, whether it be drops, sprays, douches, suction, medicated tampons, ionization, diathermy, irradiation, vaccine, or nonspecific protein therapy, will usually fail. He further states that the only possible way to overcome the mechanical obstructions caused by septal deflections or to rid the nose and sinuses of hyperplastic mucous membrane is by surgical measures. It was also stated that while it is true that all cases attacked surgically are not cured or greatly benefited, still the percentage of failures will be much less than by other methods of treatment. If not, the fault is with the operator rather than the operation.

It seems difficult to conceive of a series of 200 consecutive cases of chronic sinusitis without a possibility of the existence of a large percentage of allergy cases among them. Certainly wherever there is polypoid change in the nose and paranasal sinuses there is likely to be an allergic process. In some instances complicating infection may be present. It seems, however, that it would be extremely difficult to obtain results in these cases without proper allergic management, even though extensive surgery is performed.

Among the 200 cases operated upon by McKenzie, 101, or 53.5 per cent were considered cured; 82, or 45 per cent showed improvement of some degree of their symptoms, some slight, others very marked. Six, or 3 per cent, were unimproved.

Allergic Diseases of the Ear. Dean, L. W., Agar, J. S., and Linton, L. D.: Laryngoscope **47**: 707, 1937.

Dean and his coworkers give an excellent review of the literature covering the occurrence of Meniere's syndrome as a manifestation of allergy. The occurrence of ear symptoms in conjunction with mucosal tests, the leucopenic index, and with allergic contact were enumerated as follows: stuffiness or fullness in one or both ears, subjective loss of hearing, shooting or dull pains in the ears, itching or formication in ears, continuous high pitched tinnitus, vertigo, nausea, hyperacusis, and syncope.

Respiratory Allergy, The Incidence of Other Associated Manifestations. Hansel, F. K.: Lancet **57**: 83, 1937.

The relation of respiratory allergy to other manifestations of the disease was discussed by Hansel. These studies on the association of the various manifestations of allergy show the common occurrence of this condition in multiple rather than in single form. The patient usually presents himself for diagnosis and treatment for that manifestation which predominates the clinical picture. Associated manifestations of lesser importance, therefore, should not be overlooked. The patient with perennial nasal symptoms of allergy may have hay fever in the spring, summer, or fall. The hay fever symptoms may predominate the clinical picture while the nonseasonal symptoms may be mild or severe. If mild, attacks may be considered as acute rhinitis. Patients with perennial nasal symptoms may have asthma either with hay fever or only during the winter months. It is

important to emphasize also that allergic bronchitis not infrequently accompanies nasal allergy during the winter months without any very definite evidence of true asthma. The nasal manifestations of allergy in children are frequently overlooked unless associated with asthma. The patient whose respiratory symptoms consist only of hay fever may have allergic headache or gastrointestinal allergy or some form of skin allergy at other times of the year. Gastrointestinal allergy or allergic headache may, on the other hand, appear as the predominating symptom. Nasal symptoms may be associated in mild degree. The diagnosis of nasal allergy is always good presumptive evidence that these other manifestations are also of an allergic nature. Such manifestations as allergic headache, gastrointestinal allergy, and skin allergy are most frequently caused by hypersensitiveness to foods. The association of these manifestations with the respiratory types of allergy always suggests very strongly that foods also play an important part as etiologic factors. From these studies it is evident, therefore, that most allergic patients are affected with multiple manifestations, all of which must be considered in the clinical picture from the standpoint of diagnosis as well as treatment.

Asthma and Allergic Rhinitis from Molds. Feinberg, S. M.: Lancet **57**: 87, 1937.

Feinberg found that air-borne spores of fungi constitute an important group of causes of allergy of the respiratory tract. He pointed out that there is a decided tendency toward seasonal aggravation in this type of allergy. A series of 90 cases of mold hypersensitiveness was analyzed. Sixty were treated with a specific fungus extract with satisfactory results in most of them. Feinberg believes that mold allergy is not a rarity but is a common entity. In his experience, in Chicago and vicinity, it ranks next to pollen as a cause of nasal allergy.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

Human Passive Transfer Antibody. II. Neutralization of Antigen. Schmidt, W. M., and Lippard, V. W.: Am. J. Dis. Child. **54**: 777, 1937.

The authors were interested in the ability of the passive transfer antibody to neutralize its specific antigen. In mixtures containing an excess of antibody over antigen as shown by their titration method, such neutralization was demonstrated in 12 out of 13 observations. To demonstrate neutralization, both naturally sensitive and artificially sensitized skin sites were used. Adequate controls were afforded by mixtures of antigen with saline and with unrelated serum and by the specific serum alone with no antigen present.

The antigens neutralized were egg white, peanut, cod-fish, horse dander, and ragweed. When mixtures containing an excess of antigen over antibody were used, neutralization occurred in some instances and not in others, apparently depending upon the amount of the excess.

Demonstration of neutralization of antigen by specific antibody is taken to eliminate from consideration a point which had been emphasized as one of the differences between anaphylaxis and human allergy; namely, the absence of such neutralization in human allergy. Harley also succeeded in demonstrating neutralization of pollen antigen by specific serum but failed to define the quantitative factors underlying the phenomenon.

Heat caused a loss of the sensitizing power of the serum but did not destroy its ability to neutralize specific antibody even after being kept at 56° Centigrade.

The Nervous Factor in Juvenile Asthma. Clarkson, A. K.: Brit. M. J., 1937.

From a study of 300 cases of asthma seen in general practice, the author discusses the nervous factor in 187 cases whose ages ranged from two to twenty years. He found that the psychologic element was present in almost every case, the factors governing it being the nature of the inheritance and environment, "the degree of allergic thraldom," and the duration of the asthma.

Allergy carries with it certain psychologic limitations, even before the allergic state is manifested. Allergic children are oversensitive or apprehensive. In them emotional stimuli excite a diffuse way of psychic radiation for which the normal reciprocal inhibition is faulty. The resultant loss of localization of stimuli together with failure of adaptation enhances a potential overflow into autonomic pathways. However, it requires a purely physical impairment of the cortico-thalamic centers in addition to this overflow for asthma to make its first appearance. All the evidence suggests that the impairment is caused by biochemical changes associated with allergy. A purely psychic cause for the onset of asthmatic attacks was present in only 2 per cent of cases.

That allergy enhances the already existing psychic disturbance is shown by the change in behavior, both before an individual attack develops and after its appearance.

Besides such clinical evidences that allergic activity aggravates the psychic disturbance, the author feels that biochemical evidence in the form of the Prausnitz-Küstner reaction offers proof of it. Taking the Prausnitz-Küstner reaction as proof of the presence in the circulation of "sensitization substances" apparently capable of producing gross psychologic disorders, he cites an instance in which, by hypnosis, he caused a negative reaction on an intradermal test to egg to develop in a patient who previously and subsequently gave a markedly positive test to egg.

The asthmatic child has not only a psychic handicap but also a physical one. The latter aggravates the former and there result fear complexes related to physical insecurity. An aura of invalidism may result. The child compensates for his physical inferiority by superior scholastic achievement. Seventy-five per cent of the group were above average in scholarship and only one per cent was below.

Once asthma is well established, all the characteristics of a conditioned reflex are acquired, and now memory of a previous attack is sufficient stimulus to precipitate another attack. Somatic stimuli also suffice to stimulate the well-established pathway. For example, recalling an emotional disturbance, the suggestion of artificial flowers or a distended stomach may all be the provocative factors in a sensitized individual. On the basis of the conditioned reflex, there may result purposive simulation, hysterical habituation, or voluntary reinforcement of asthma. A stage may finally be reached where the "allergic catalysts" (necessary for the onset of the first attacks) are no longer needed for asthma to develop, and the habituation reflex may be used independently of its allergic origin.

It is important, therefore, not only to consider the allergic or biochemical factors, but also social and environmental maladjustment. Removal of the offending allergens alone may enable the patient to attain psychic poise and readjustment, but this and other treatment must be carried out early if an habituation reflex is to be avoided.

Concerning Eczema in Infants and Small Children, Its Cause and Treatment. Schneider, E.: Med. Klin. **40**: 1327, 1937.

The author discusses various views on the etiology of seborrheic dermatitis, true infantile exudative eczema, and neurodermatitis and their combined forms. She gives her own views on what parts constitution, disordered metabolism of various food components, sensitization, and deficiency in skin-vitamin play. A program of

treatment is outlined for infants with these disorders, which consists in a diet free from salt, fat, and animal protein for a period of four to six weeks. Fruits, vegetables, and cereals are largely used with added protein from "Materna," a bran derivative. Later, the gradual addition of milk, fat, and salt is made and may cause a flare-up which is temporary. Meat and curds, however, may have to replace milk.

This diet is indicated in all cases save those forms of seborrheic dermatitis which depend on a deficiency in the skin-factor and in atrophic infants. The former require a protein-rich diet with large amounts of skin vitamin in the form of 100 to 250 gm. of liver daily. The latter are given a concentrated and adequate diet and lose their allergic response with improved nutrition.

Concerning Immunity to Vaccination at Birth. Andersen, O.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **90**: 459, 1937.

Considerable difference of opinion has existed regarding the immune status of the newborn of vaccinated mothers. Working with rabbits, the author found that all the offspring of mothers vaccinated one to six months before pregnancy showed some virus neutralizing antibody one to two days after birth. Vaccination was unsuccessful for as long as three weeks after birth. At three months of age no virus neutralizing antibody could be demonstrated in the serum.

In the offspring of unvaccinated mothers, no neutralizing antibody could be demonstrated and on vaccination all had marked reactions and died in four to five days. It is concluded that in newborns of unvaccinated mothers, vaccination will result in a reaction like that of older children or even more intense.

Miscellaneous

Disorders of the Nervous System in Serum Sickness. Schipkowensky, N.: Arch. f. Psychiat. **106**: 779, 1937.

Although cases of nervous system lesions following serum sickness are infrequent in the literature (some 80 cases reported), the fact that the author observed four inclines him to believe the condition occurs more than such statistics indicate. He makes a thorough analysis of the condition and of many observations and the following are the most significant.

Children are rarely affected, most patients being over twenty-one years of age, although it is children to whom serum is most frequently given. This apparently has nothing to do with nerve resistance since lesions of poliomyelitis are so common in earlier years. The lesion is almost always a polyneuritis affecting the brachial plexus far more frequently than other parts leading to muscle weakness. Sensory disturbances as hyperesthesias are common. Other less frequent manifestations are amnesia and other central nervous system symptoms, trophic disorders, and muscle spasm. Vasomotor and secretory disorders have not been observed.

No adequate explanation of the mechanism of the condition is available, although several have been advanced. The most plausible is that of an edema which particularly attacks the region of the exit of nerves that form the brachial plexus from the spine. Although patients usually recover, it may take months. Physiotherapy and the usual treatment for peripheral neuritis is the indicated treatment.

Hydroarthrosis of Allergic Origin. Service, W. C.: Am. J. Surgery **37**: 121, 1937.

The occurrence of hydroarthrosis is probably a much more common manifestation of sensitization than the medical literature would seem to indicate. Hydroarthrosis occurs in most cases in association with some other allergic manifestation

and is relieved by measures that cure the accompanying conditions. Four cases are cited in which gastrointestinal symptoms were present and preceded by a considerable time the appearance of joint symptoms. Food allergy is unquestionably of great importance. In the four cases cited in which allergic histories were accompanied by joint symptoms, relief was secured by correcting the existing allergy.

The Therapy of Migraine. Schick, A.: Wien. klin. Wchnschr. **50**: 1205, 1937.

The author discusses typical migraine from other forms of headache and selected a group of 74 cases in which no form of therapy including antiallergic measures was of benefit. He treated these with magnesium sulfate. The rationale for this form of treatment was the experience of others in its use in various spastic conditions such as tetanus, angiospasms, bronchial asthma, intermittent claudication, and angina pectoris.

A 50 per cent solution was used intravenously beginning with 2 c.c. and working up to 5 c.c. Twelve injections were given twice a week. The drug was administered very slowly and the only untoward effect was a general feeling of warmth.

Of the 74 patients treated during a period of a few years, four had no return of headache, 45 were decidedly benefited, and the remaining 25 essentially unaffected.

Calcium in the Treatment of Allergy. Rudolph, J. A.: M. Rec. **244**: 192, 1937.

Calcium was administered to thirty-six allergic patients over a period of one year or more. The clinical disorders included asthma, asthmatic bronchitis, perennial vasomotor rhinitis, and hay fever. Three grams of di-calcium phosphate daily were given to each patient. The drug was effective in bringing about improvement in seven of twenty-five adults (28 per cent) and six of eleven children (55 per cent). All had been treated for varying periods previously, and none had done well on the usual allergic regime. The longer the period of calcium administration, the better the results. Previous reports on the therapeutic ineffectiveness of calcium represent, for the most part, conclusions drawn after too short a period of observation. Calcium should be given for an indefinite time in allergic disorders.

The False "Acute Abdomen." II. Henoch's Purpura and Abdominal Allergy. Althausen, T. L., Deamer, W. C., and Kerr, W. J.: Ann. Surg. **106**: 242, 1937.

Eight cases of Henoch's purpura and of abdominal allergy are reported. Six of these patients had acute abdominal pain as the presenting symptom and at various hospitals had undergone nine abdominal operations for their attacks. The distinguishing features of the clinical picture and laboratory data in Henoch's purpura and the characteristics of the allergic individual are discussed. Intussusception as a rare complication of Henoch's purpura requiring surgical intervention is considered.

A Diagnostic Intradermal Reaction with Bowel Antigen. Paulson, M.: J. A. M. A. **109**: 1880, 1937.

A technique has been evolved for the practical preparation of a bowel antigen for intradermal use. A positive response to the antigen indicates the presence of the virus of venereal lymphogranuloma in the material from which the antigen was made. While the indication of the presence of the virus of venereal lymphogranuloma in the bowel is not proof of etiology of the colitis which it accompanies, experimental and clinical evidence strongly suggests this relationship.

Criteria for interpretation of the intradermal tests have been developed.

By tests with this antigen, it is hoped to narrow further the classification nonspecific ulcerative colitis, the cases in which there are indications of the virus of venereal lymphogranuloma in the intestine being separated from those in which there are not.

Book Review

ALLERGY, HAY FEVER, MIGRAINE AND OTHER CLINICAL STUDIES. By A. J. Auld, M.D., 1936, pp. 254. H. K. Lewis & Co., London.

This book is a compilation of a series of lectures and articles presented by the author over a period of some twenty years. Only one chapter is a new contribution. This deals with the nature of allergy with remarks on treatment and is but four pages in length.

The author is a well-known proponent of peptone therapy in the treatment of asthma. This form of therapy is reviewed and data in support of it assembled in the first chapters. Beyond that, the book does not justify its title or existence. The subject of hay fever stated on the cover is dealt with in four pages, migraine gets eleven pages, and from there on succeeding chapters are devoted to such subjects as fever therapy, acute pneumonia, a method of examining the pulmonary apex, acute nephritis, calomel, as a diuretic action in dropsy, a case of hystero-epilepsy and other unrelated matters. The book has little place in the serious literature on allergy.